Cologuard

Advisory Committee Meeting

FDA Molecular and Clinical Genetics Panel

March 27, 2014

Introduction

Kevin Conroy

Chairman & CEO

Exact Sciences Corporation

Agenda

Colorectal Cancer Background	**Bernard Levin, M.D.** *Univ. of Texas M.D. Anderson Cancer Center*
Rationale for Stool DNA	**David A. Ahlquist, M.D.** *Mayo Clinic*
Test Description and Development	**Graham Lidgard, Ph.D.** *Exact Sciences*
DeeP-C Pivotal Study	**Thomas F. Imperiale, M.D.** *Indiana University*
Post-Approval Study	**Sandra Statz** *Exact Sciences*
Clinical Benefit	**Sidney J. Winawer, M.D.** *Memorial Sloan Kettering Cancer Center*

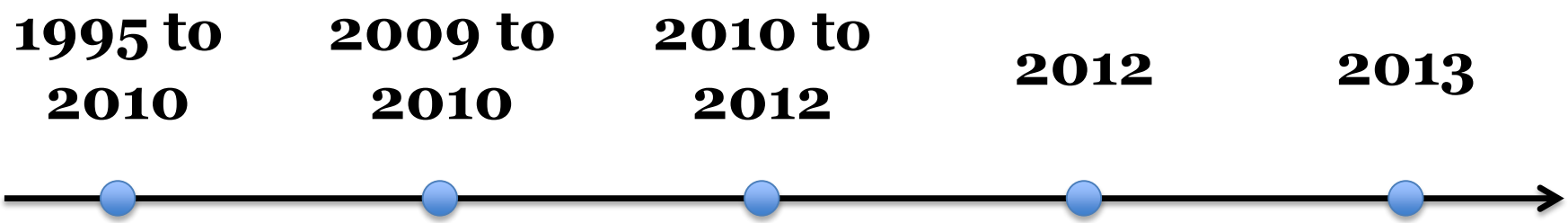
Additional Speakers

Expert	Background
Steven Itzkowitz, M.D.	Gastroenterologist/IBD & Cancer *Mount Sinai Hospital*
Harvey Kowaloff, M.D.	Primary Care Physician *Saint Anne's Hospital*
Charlotte Owens, M.D.	OB/GYN *Morehouse School of Medicine*
Philip Lavin, Ph.D.	*Boston Biostatistics Research Foundation*
Tarun Chandra, Ph.D.	*EmpiriQA LLC*

Cologuard Summary

- Colorectal cancer is a major health problem
  - >50,000 CRC deaths forecast in the US in 2014
- Screening works but compliance is suboptimal
  - Screening reduces mortality and incidence
  - ~30 million Americans are *not* current with screening
- Cologuard is a stool-based DNA test
- The pivotal study of Cologuard met its endpoints
  - >12,000 subjects enrolled in clinical study (DeeP-C)
  - 92% cancer sensitivity & 69% high grade dysplasia sensitivity
  - 87% specificity & 99.94% negative predictive value for cancer
- Benefits outweigh risks

Cologuard Development



Cologuard Indications for Use

Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool.

A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. Cologuard is not intended as a replacement for diagnostic colonoscopy.

Cologuard is intended to be used in conjunction with colonoscopy and other test methods in accordance with recognized screening guidelines. A positive result in Cologuard, as with any screening test, should be followed by colonoscopy.

Cologuard is intended for patients who are typical candidates for colorectal cancer screening, adults of either sex, 50 years or older, who are at average risk for colorectal cancer.

Colorectal Cancer Background

Bernard Levin, M.D.

Professor Emeritus

University of Texas M.D. Anderson Cancer Center

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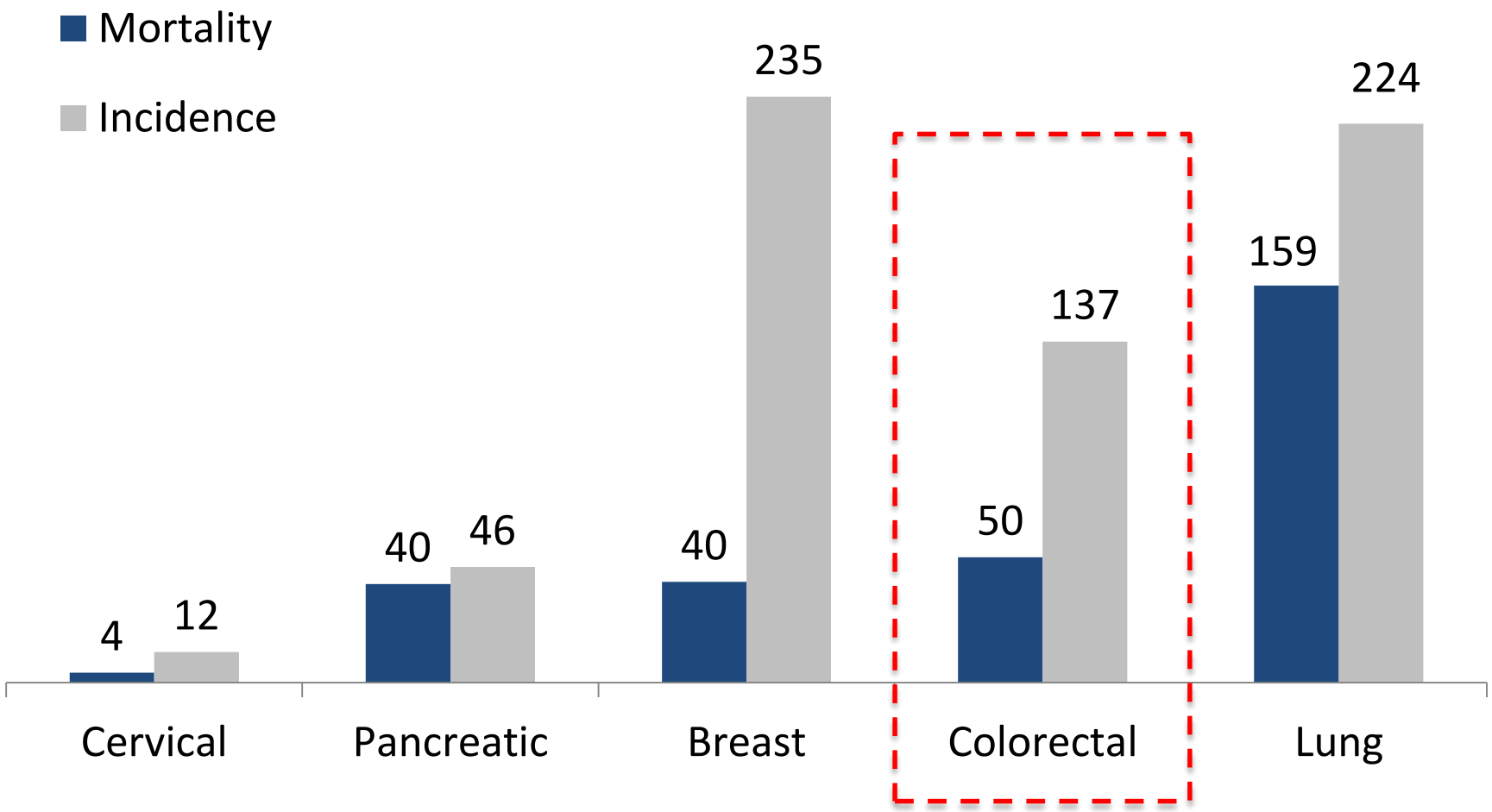
Overview

- **CRC is a major public health problem**
- **Biology**
  - Natural history favors screening
  - Pre-cancer (adenoma) progresses to cancer slowly
- **Screening**
  - CRC screening lowers incidence and mortality
  - Current non-invasive screening tools beneficial but performance characteristics suboptimal
  - A sensitive non-invasive screening option is needed that accurately detects:
    - Early stage cancers
    - Important pre-cancers

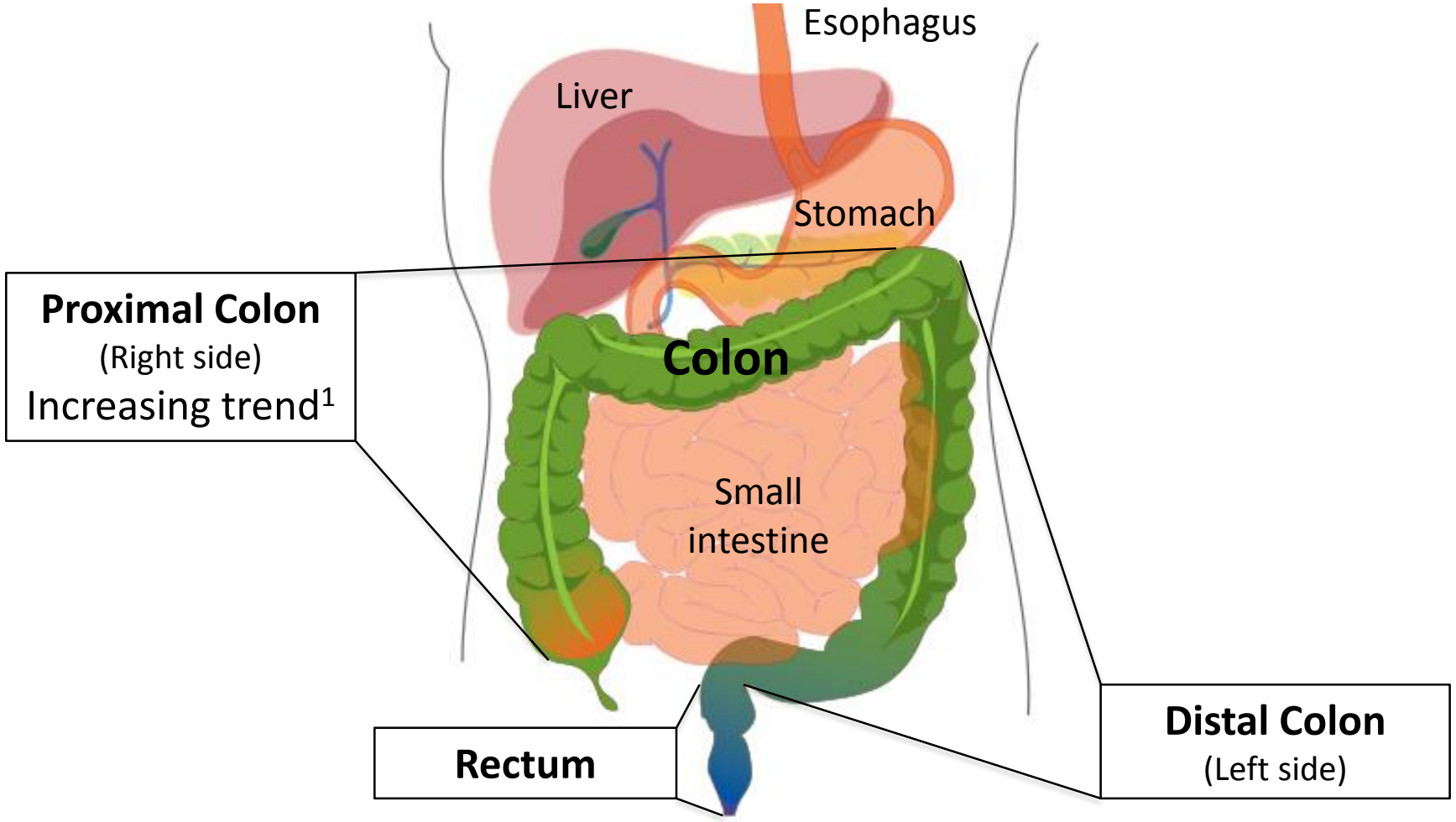
US Cancer Mortality and Incidence[1]

(Thousands, 2014 estimate)



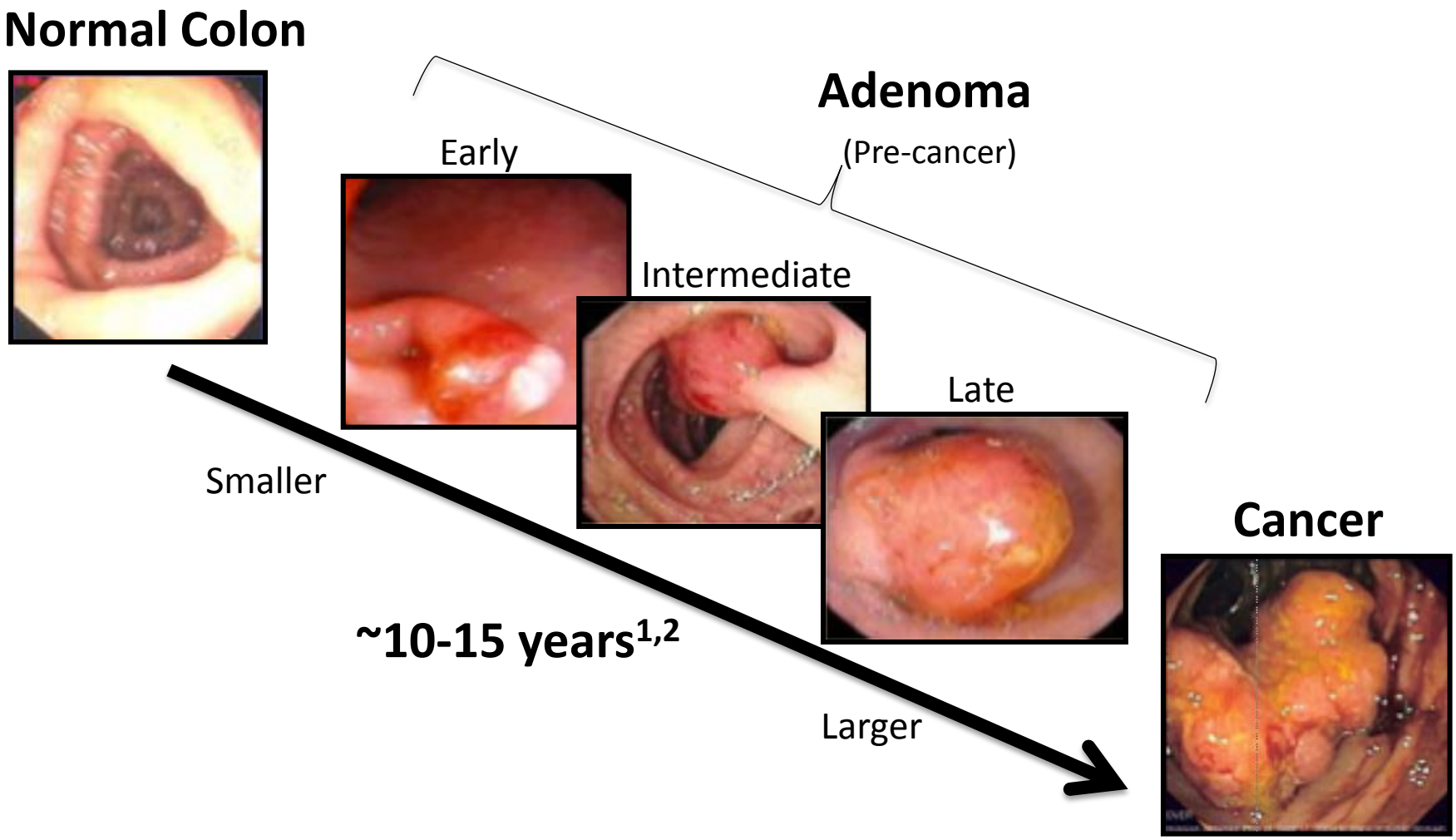
[1]ACS: Cancer Facts and Figures 2014

Colorectal Location Matters



[1]Meza, et. al., Cancer Research (2010)

Natural History of Colorectal Neoplasia



[1]Amersi et. al., Clin Colon Rectal Surg (2005)
[2]Zauber et. al., New Eng J Med (2012)
Photo source: Rozen, Young, Levin, Spann, *Colorectal Cancer in Clinical Practice* (2002)

Adenoma Characteristics

Size

- Diameter

Larger adenomas are more likely to progress to cancer

Type

- Tubular
- Tubulovillous
- Villous
- Sessile Serrated

Dysplasia
(Cellular abnormality)

- Low grade
- High grade (HGD) = carcinoma in situ

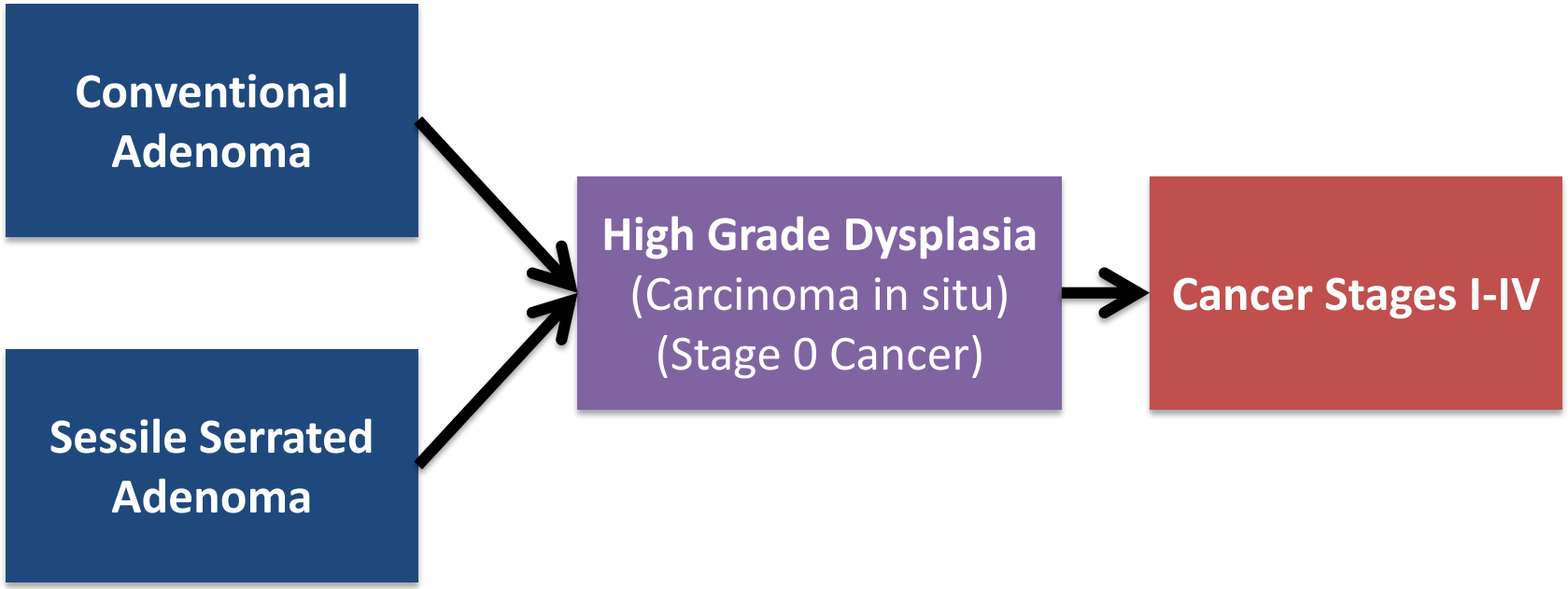
HGD is most likely to progress to cancer

Advanced Adenoma (AA) Definition

Size	▪ **All adenomas ≥ 10 mm diameter**
Type	▪ **Villous component** (≥ 25% of adenoma)
Dysplasia (Cellular abnormality)	▪ **High grade dysplasia**

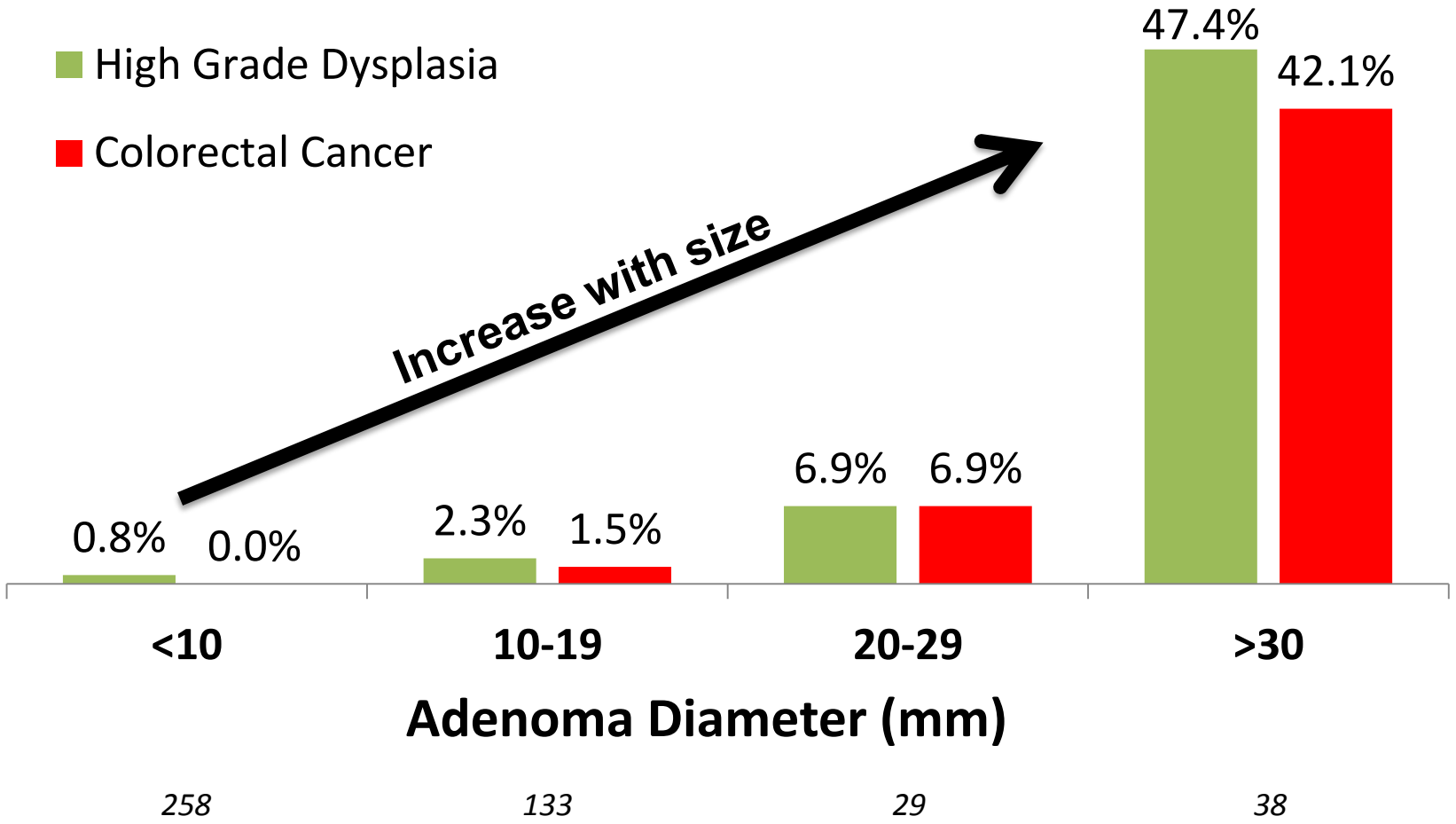
Critical Importance of High Grade Dysplasia

CRC Development Pathway[1]



[1]Makkar et. al, Cleveland Clinic Journal of Medicine (2012)

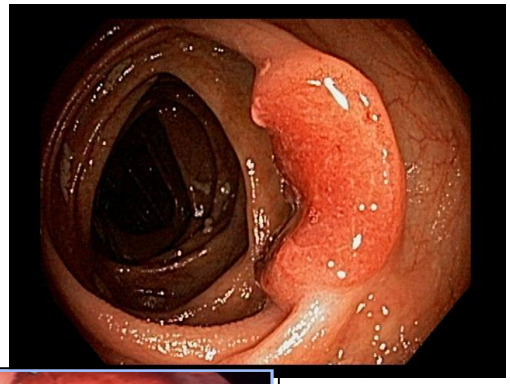
Likelihood of Adenoma to Contain HGD or CRC[1]

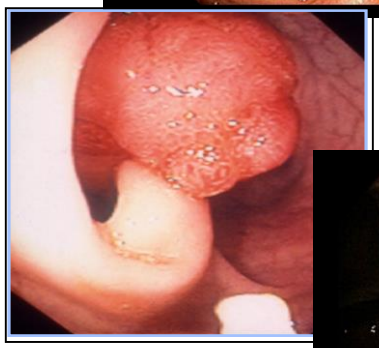


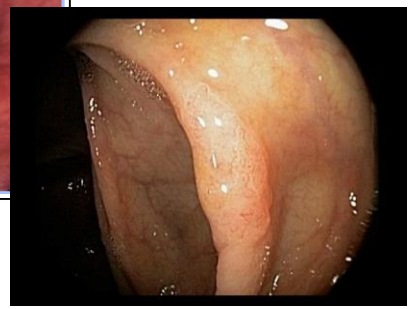
[1]Pickhardt et al. Clin. Gastro. and Hep. 2010;8:610

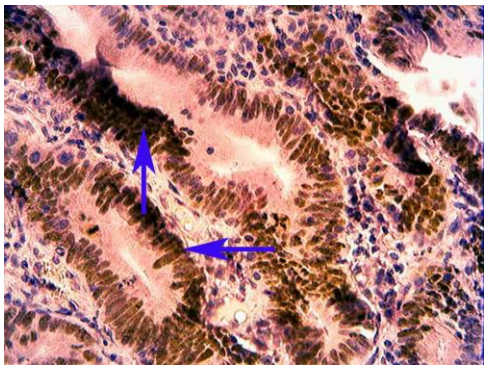
Screening: Target Lesions

- Curable stage cancer
- Advanced pre-cancer
  - Large adenoma (i.e. ≥2cm)
  - Large sessile serrated adenoma
  - High grade dysplasia

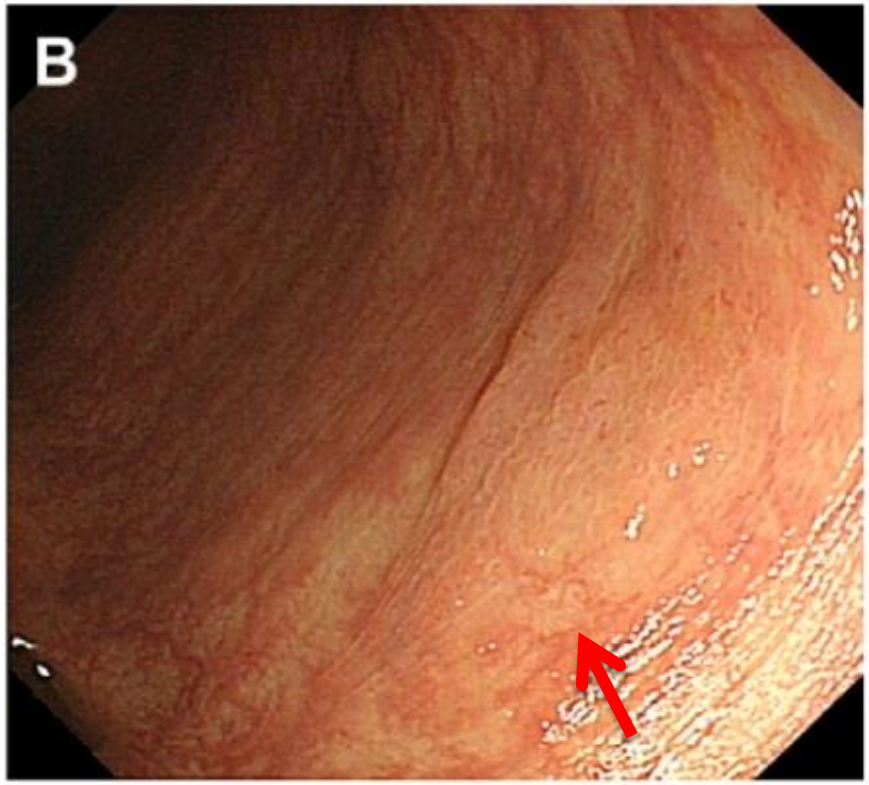








Sessile Serrated Adenoma: A Recently Identified CRC Pathway



- Cause ~1/3 of colorectal cancer[1]
- Hard to see
- Don't bleed[2]

[1]Snover DC, Human Pathology (2010)
[2]Heigh et. al., PLOS One (2014)
Photo courtesy Dr. Won Kee Song, Mayo Clinic

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CRC Screening Rationale

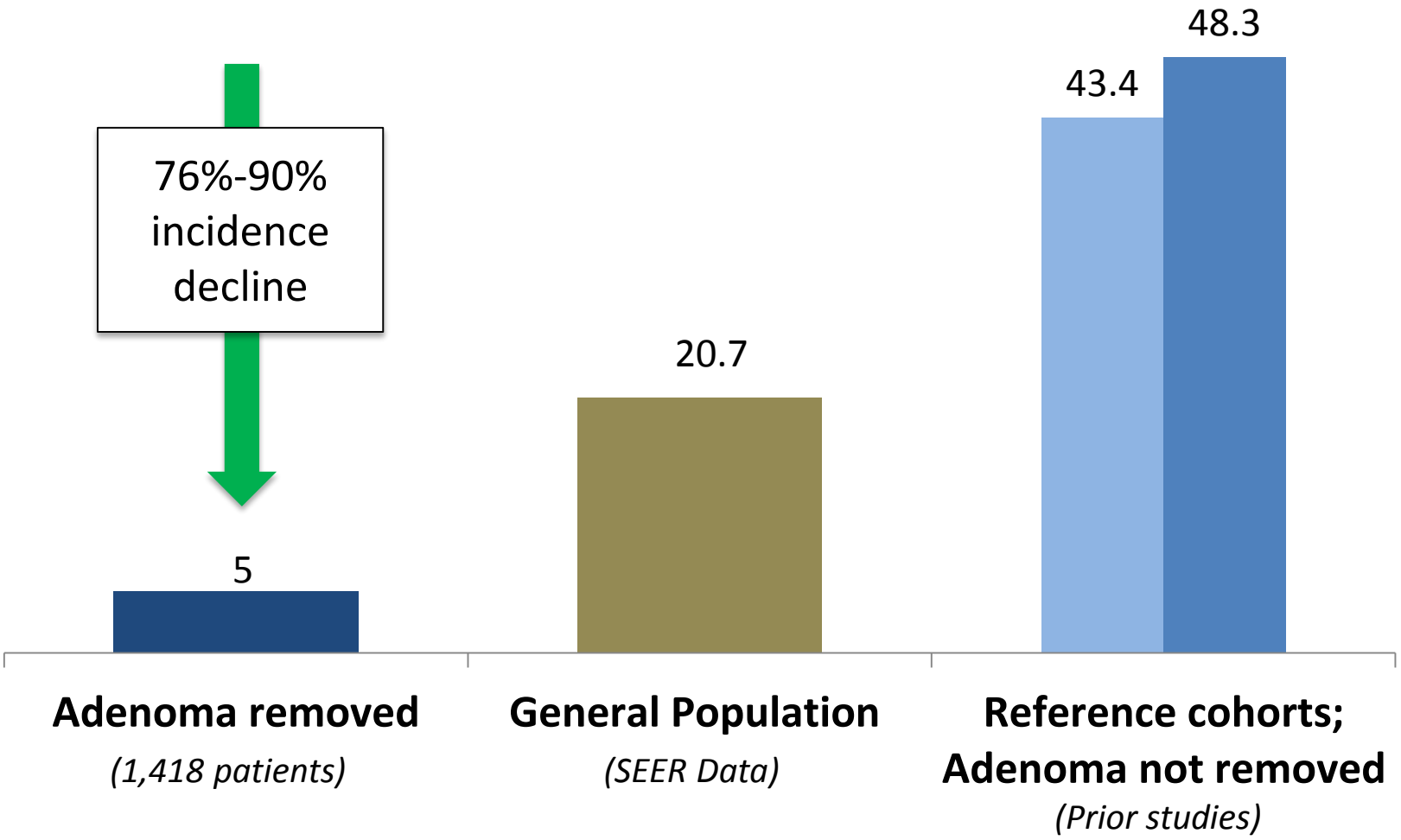
CRC is well suited to screening for two primary reasons:

1. Detection and removal of adenomas lowers incidence and mortality

2. Early detection and resection of cancer lowers mortality

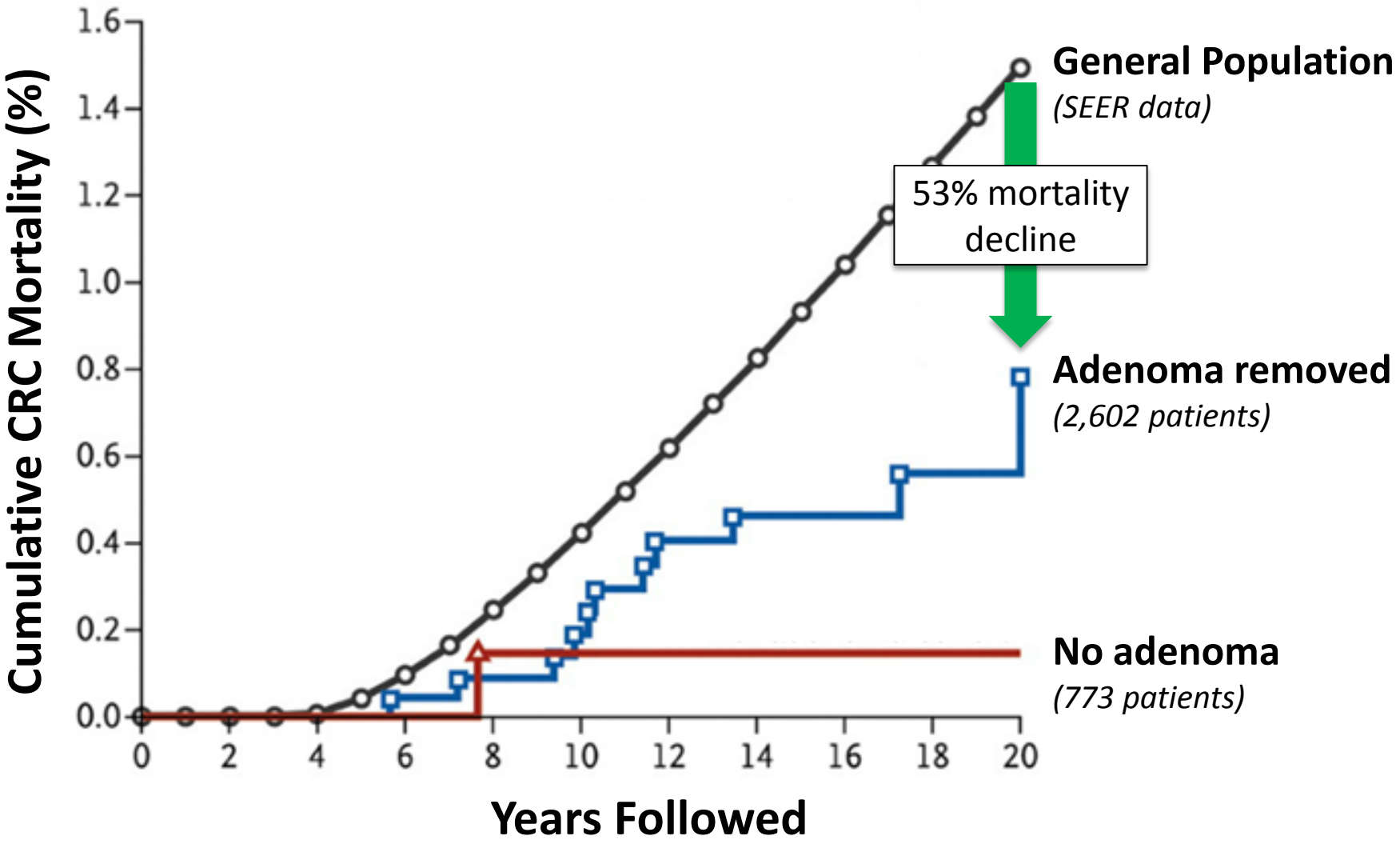
National Polyp Study: CRC Incidence[1]

(# of CRC cases over 7 years)



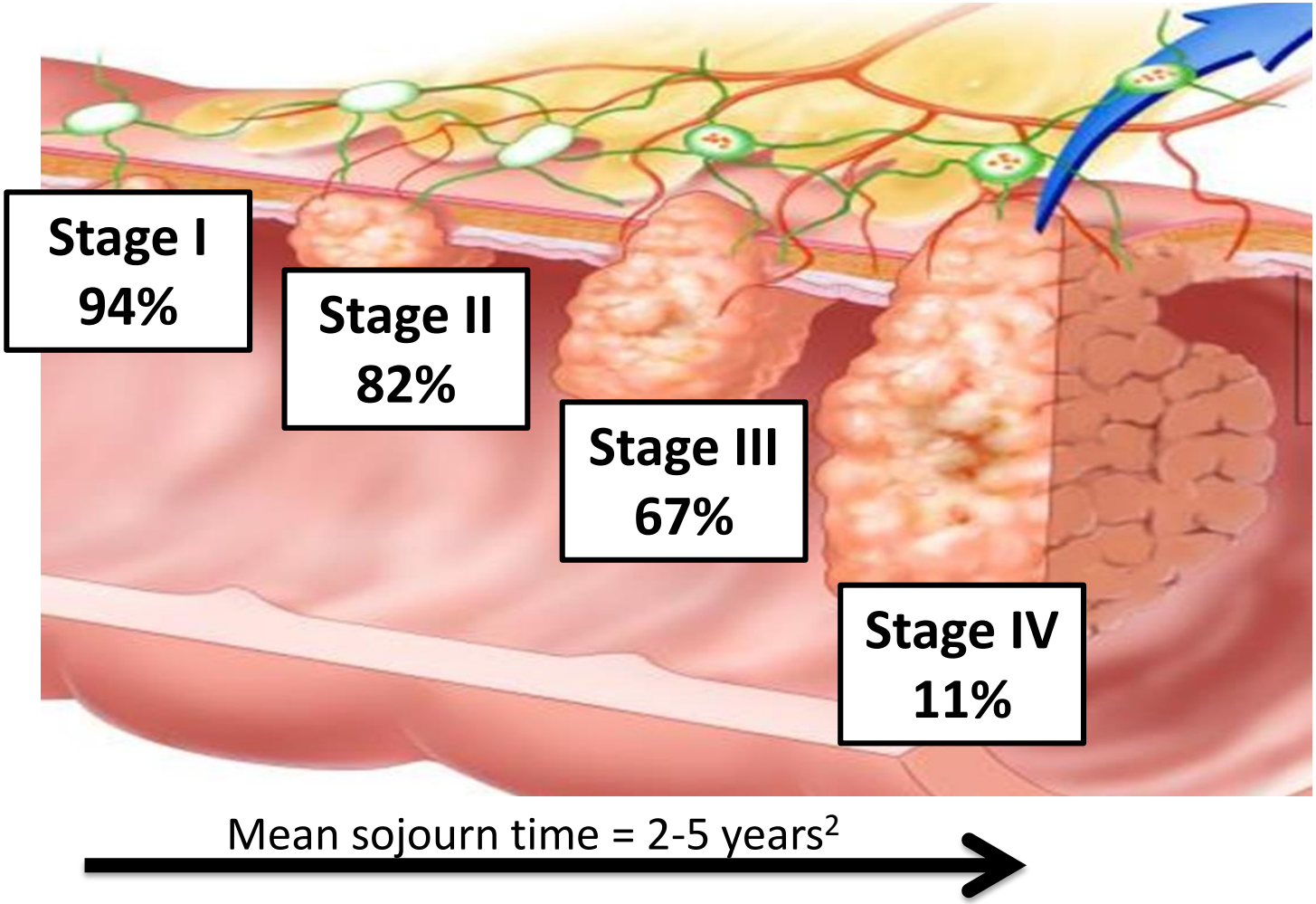
[1]Winawer et. al., New Eng J Med (1993)

National Polyp Study: CRC Mortality[1]



[1]Zauber et al., NEJM, 2012

Stages & 5 Year Survival Rates of CRC[1]



[1]Lansdorp-Vogelaar, et. al., J Natl Cancer Inst 2009; 101:1412-1422
[2]Zauber et. al., New Eng J Med (2012)
Figure from Cancer.gov

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Current Screening Tests & Performance[1]

		Sensitivity		Specificity
		CRC	AA	
Invasive Tests	Colonoscopy[1]	95%	95%	90%
	Sigmoidoscopy[1]	~50% (95% distal only)	~50% (95% distal only)	92%
	CT Colonography	96%[2]	94%[3]	86%[4]-96%[3]
Non-Invasive Tests	FIT[1]	70%	22%	95%
	gFOBT (Hemoccult SENSA) [1]	70%	24%	93%
	gFOBT (Hemoccult II) [1]	40%	12%	98%

[1]Zauber, et al., Agency for Healthcare Research and Quality (2009)
[2]Pickhardt et. al., Radiology (2011)
[3]Pickhardt et. al., New England Journal of Medicine (2003)
[4]Johnson, et. al., New England Journal of Medicine (2008)

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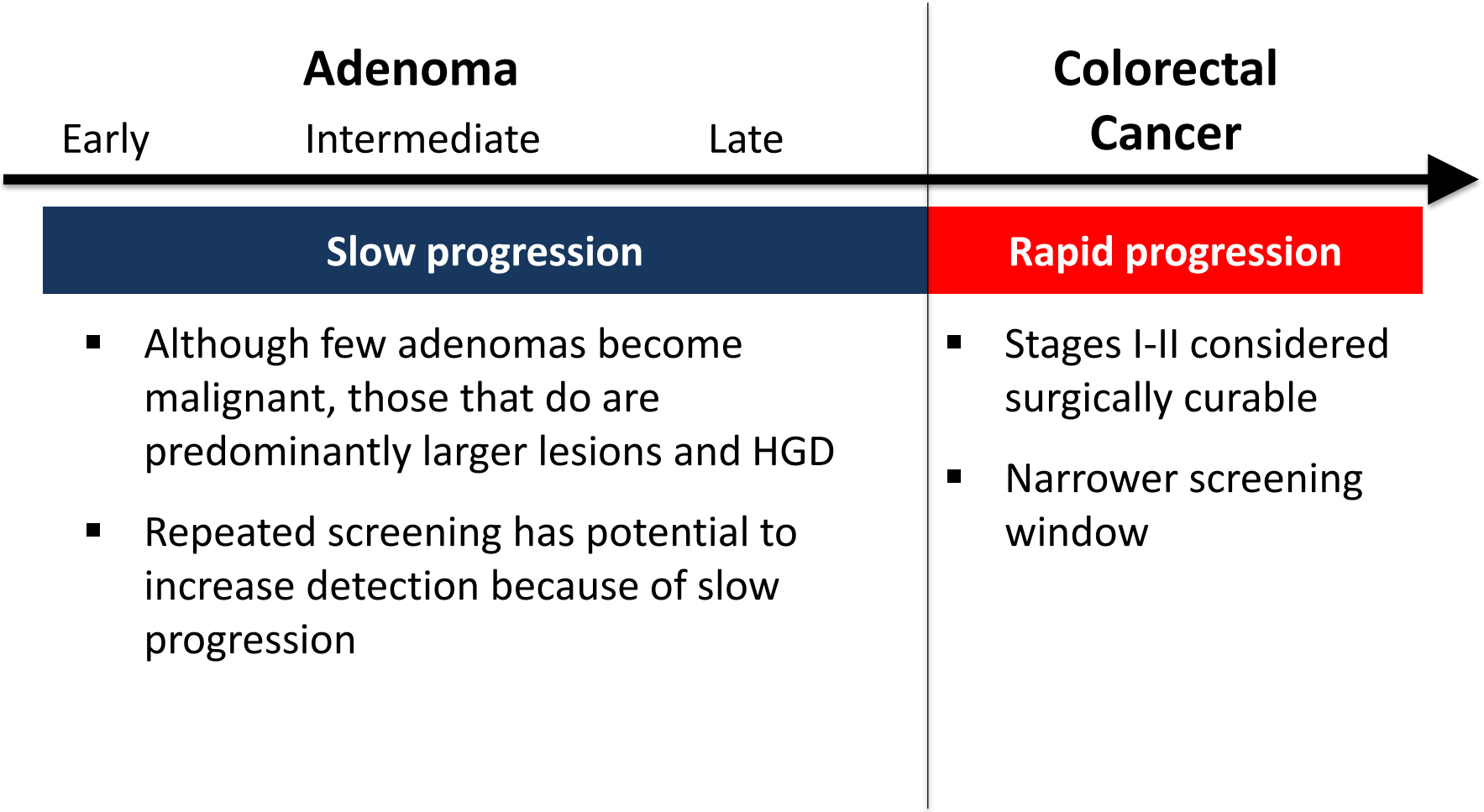
Biological Considerations for Test Performance



- Although few adenomas become malignant, those that do are predominantly larger lesions and HGD
- Repeated screening has potential to increase detection because of slow progression

- Stages I-II considered surgically curable
- Narrower screening window

CRC Unscreened Population in the US

98 million Americans 50-84[1] **X** One in three unscreened[2] **=** ~30 million unscreened

[1]*US Census Bureau (2013)*
[2]*CDC – Vital Signs (2013)*

Desired Characteristics of New, Non-invasive CRC Screening Test

- High sensitivity for early stage CRC
- Cancer detection throughout the colon
- Improved advanced adenoma detection
- Balance specificity with sensitivity
- Safe and simple to use

Stool DNA Development

David A. Ahlquist, M.D.

Professor of Medicine, Mayo Clinic, Rochester, MN

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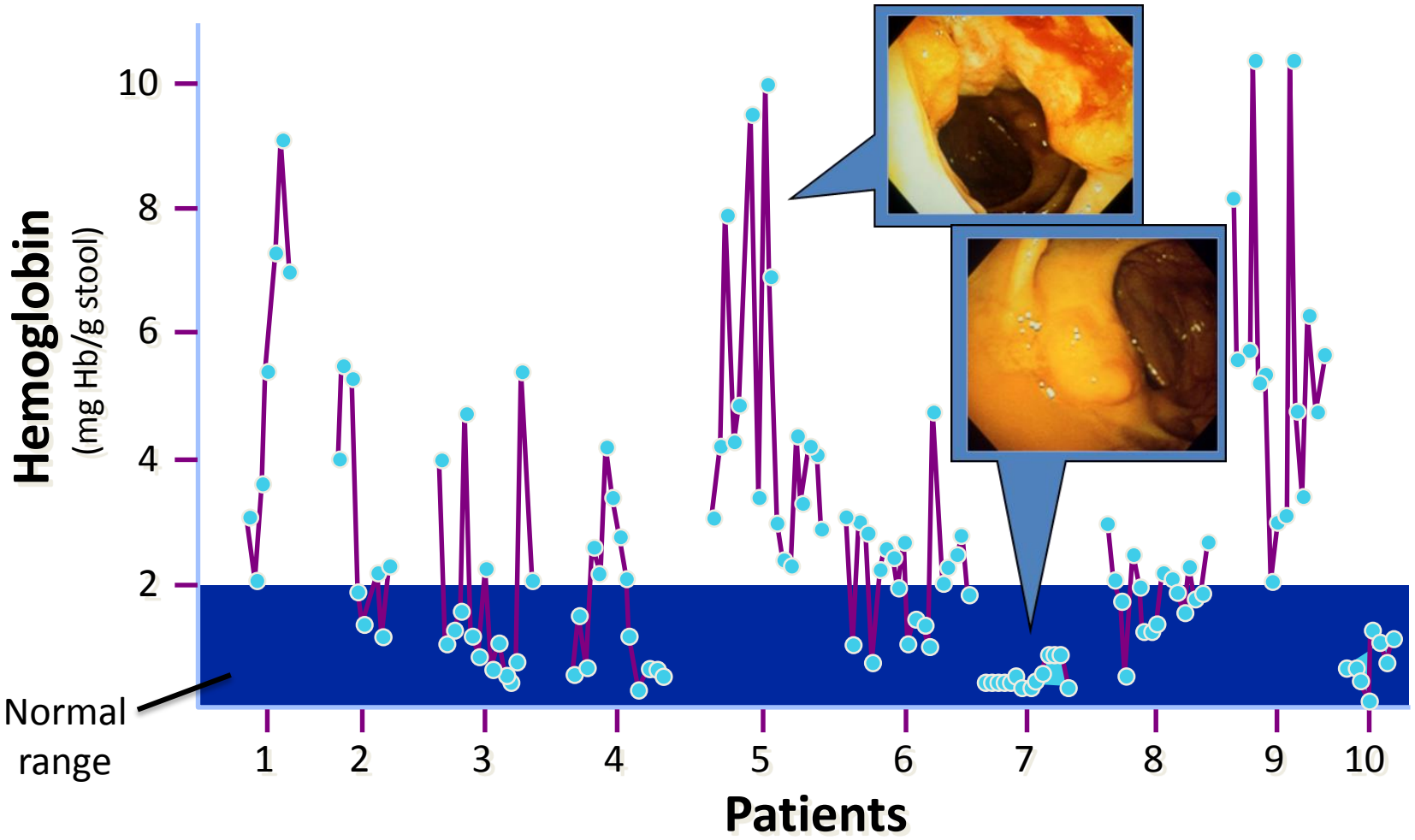
Overview

- Limitations of fecal occult blood
- Biological rationale for stool DNA as a screening method
- Early development

Occult Blood Levels for CRC Subjects Over Two Week Period[1]



[1]Ahlquist et al, Cancer 1989;63:1826

Morikawa FIT Study

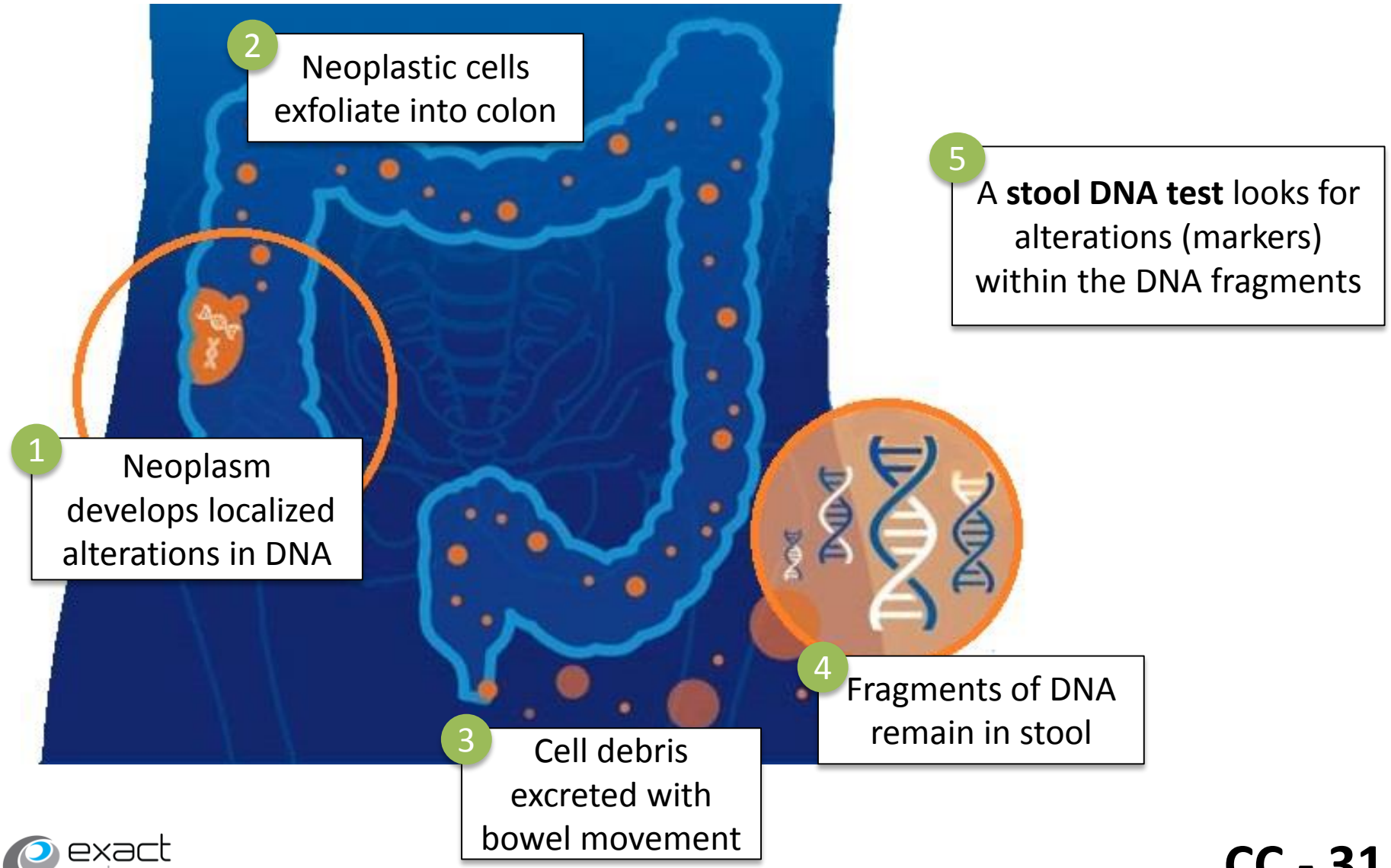
- Large average-risk cross-sectional study (21,805)
- FIT result compared to colonoscopy (reference standard)
- Detection sensitivities at 95% specificity

Cancer (77)	
All	66%
Stage I	53%
Stage II	70%
Stage III-IV	78%

Advanced Adenoma (648)	
All	22%
HGD	33%
Other AA ≥1cm	20%

Morikawa et, al., Gastroenterology 2005;129:422

Stool DNA Overview



Source: Gastroenterology. 2012;142(2)

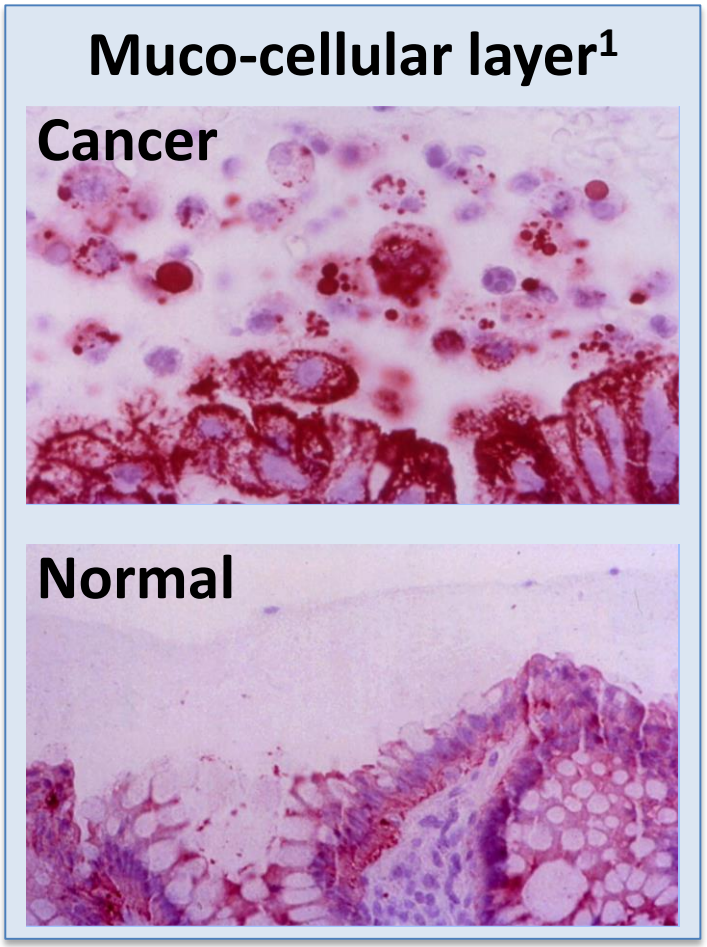
Biological Basis for Stool DNA

1) CRC and AA Exfoliation

- Abundant
- Continuous
- Cancer > normal

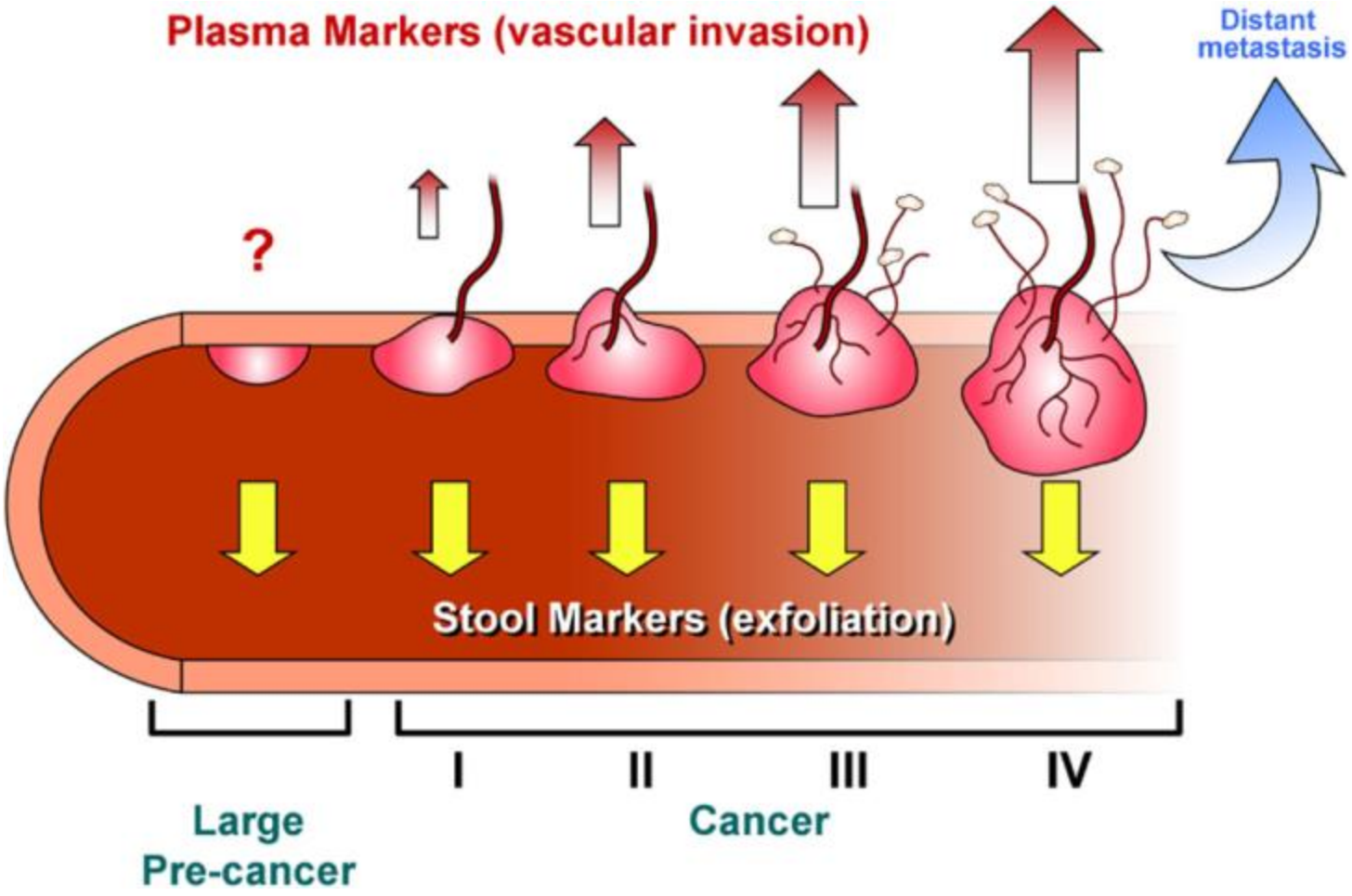
2) DNA as marker

- Signature changes
- Stable
- Amplifiable



[1]Ahlquist et al. Hum Pathol 2000 31:51

Exfoliation: A Rational Biology



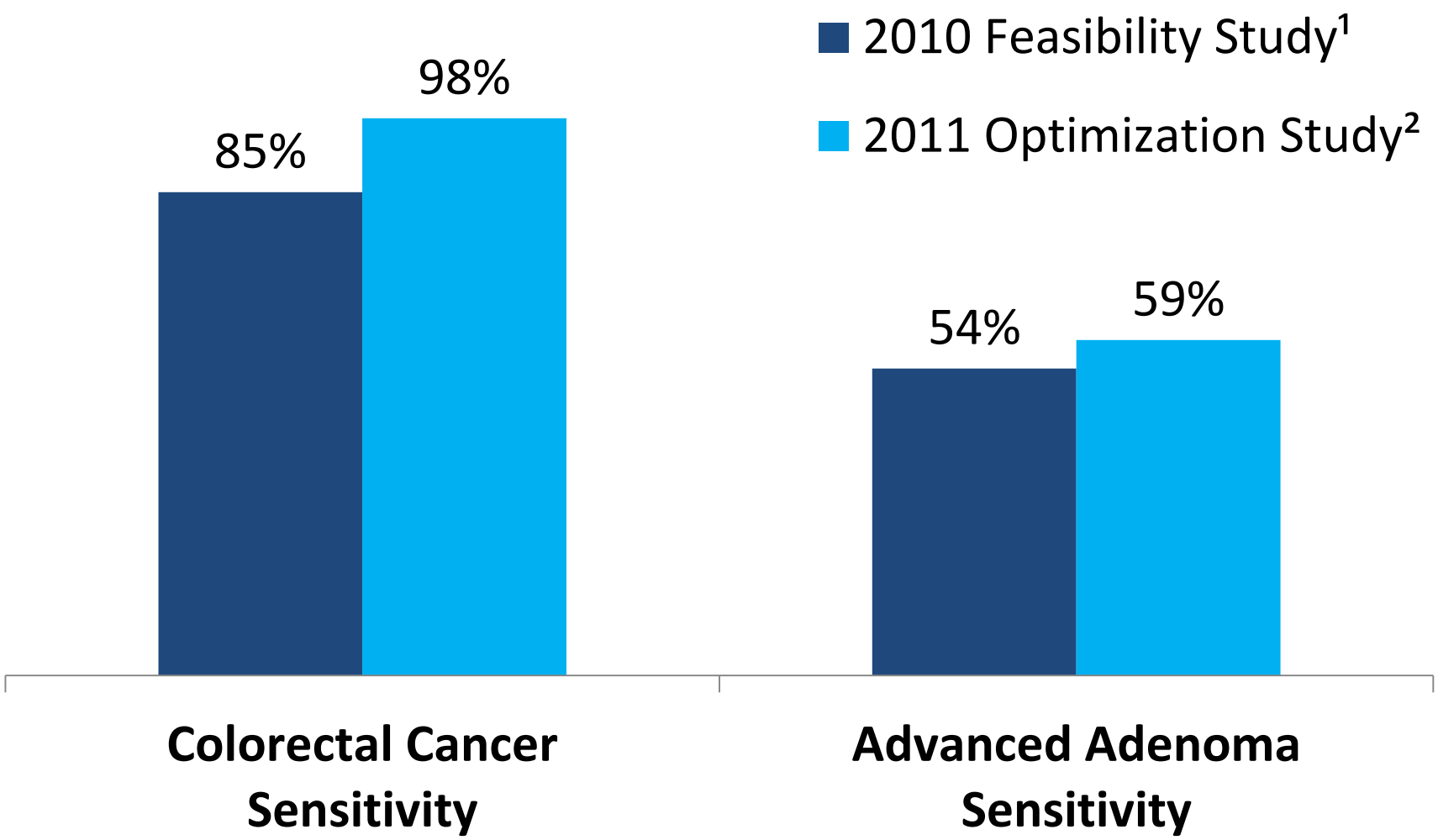
Source: Ahlquist DA et al. *Clin Gastroenterology Hepatol*. 2012;10(3);272-277.

Development Challenges

- **Identify DNA markers found in AA and CRC**

- **Accurately detect those markers in stool**
  - Stool is full of potential interfering substances
  - Significant amounts of microbial DNA in stool
  - Series of steps developed to capture pure human DNA targets before amplification

Promising Early Cologuard Results (Prototype)



[1]Ahlquist et al. Gastroenterology 2012; 142:248
[2]Lidgard G P. Poster Presented at DDW 2012, San Diego, CA, May 19-22, 2012

Evolution of Non-Invasive CRC Screening

gFOBT
(Heme)

The first non-invasive test for CRC

- Detection limited by intermittent bleeding
- 3 bowel movements
- Dietary restrictions

FIT
(Globin protein)

Launched in early 2000s

- Detection limited by intermittent bleeding
- Single sample
- No dietary restrictions

Stool DNA

Under development since 1990s

- CRC and AA continuously exfoliate cells
- Single sample
- No dietary restrictions

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Cologuard Description and Development

Graham Lidgard, Ph.D.

Chief Science Officer, Exact Sciences

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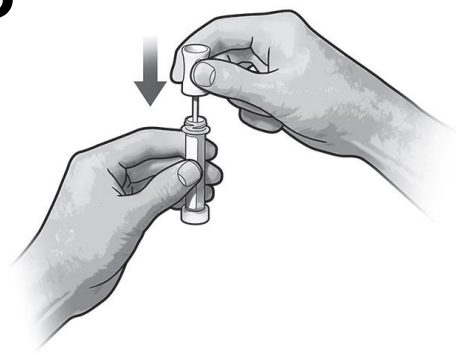
Cologuard Elements

Home Sample Collection Kit Steps

1

2

3



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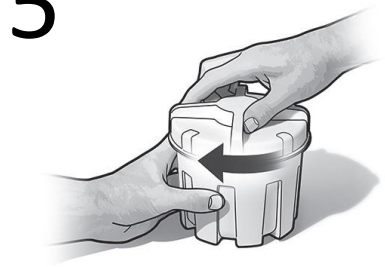

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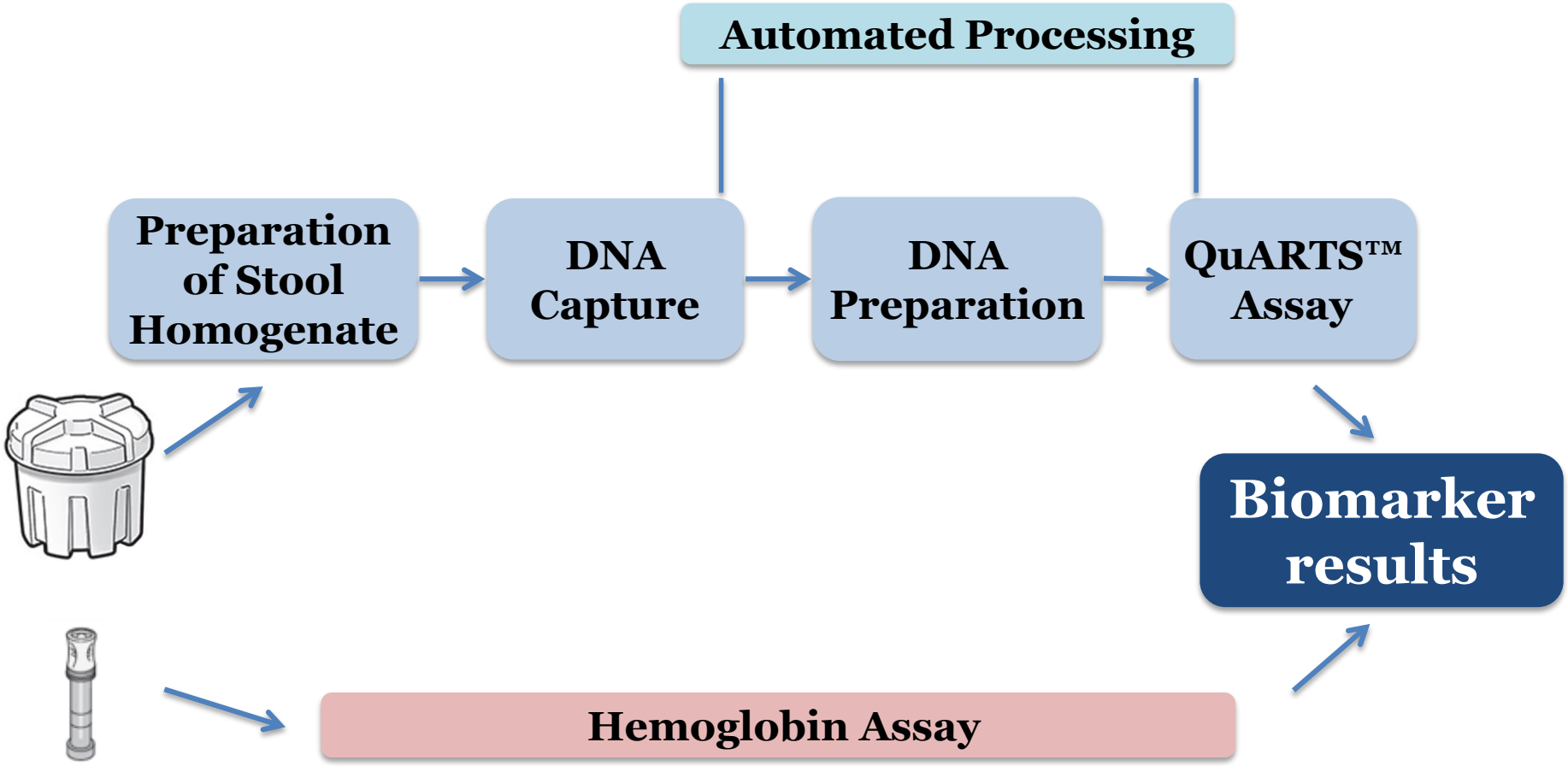
Sample Analysis Workflow



Cologuard Biomarkers

2 DNA Methylation Markers

NDRG4 and BMP3

7 DNA Mutation Markers

All KRAS

DNA Normalization Marker

Beta Actin (Quantitative DNA)

Molecular Assay (DNA)

Fecal Hemoglobin Marker

FIT

Hemoglobin Assay (Protein)

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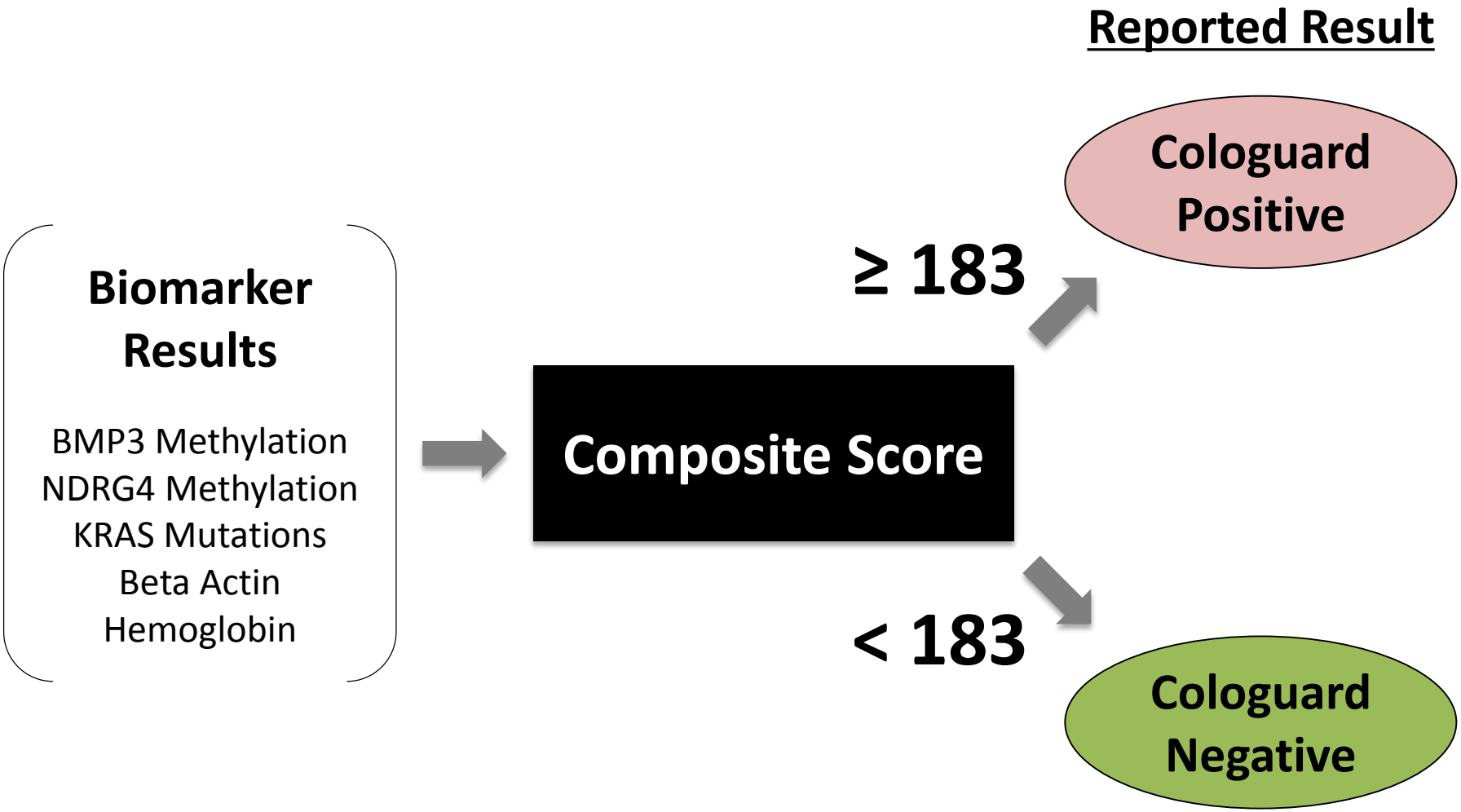
Cologuard Algorithm



Cologuard Development Studies

Optimized and automated Cologuard assay

- ~2,000 samples
- QuARTS multiplex
- ImmunoAssay
- ~250 CRC cases
- ~130 AA cases

Algorithm Defined

- ~1,000 samples
- Statistical cross-validation
- Algorithm locked
- 93 CRC cases
- 114 AA cases

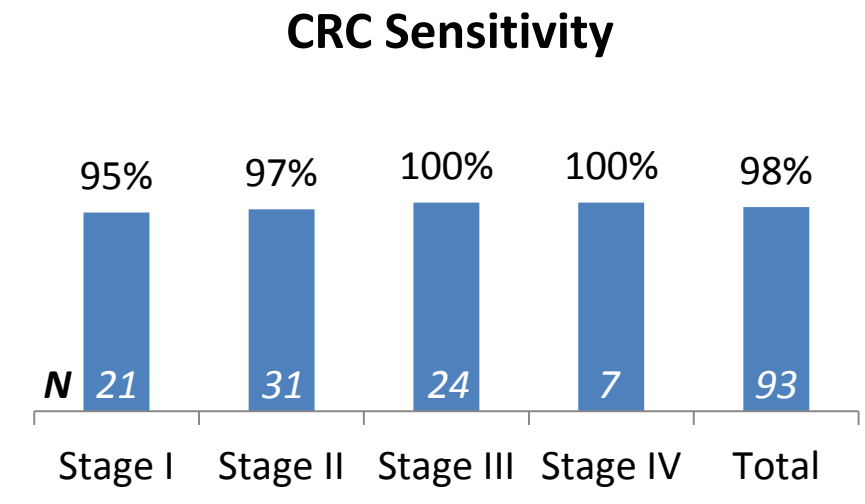
Cologuard Validation

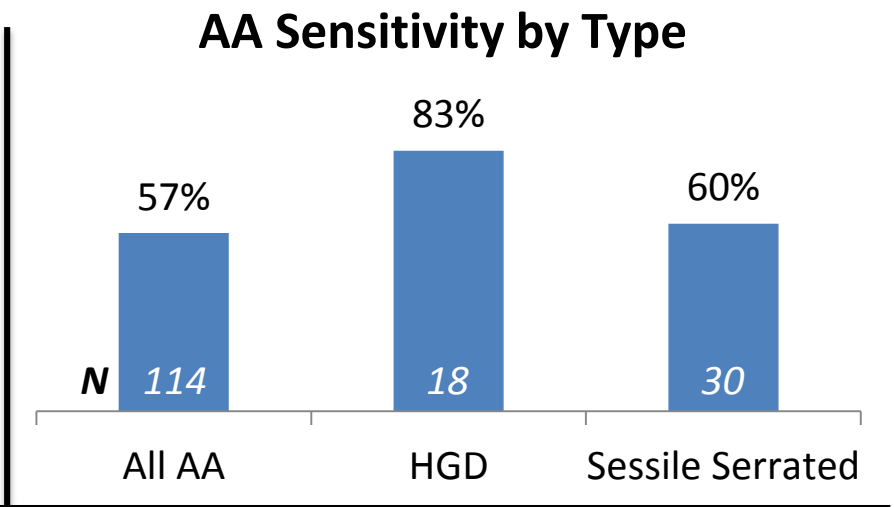
- ~10,000 samples
- DeeP-C clinical study
- 65 CRC cases
- 760 AA cases

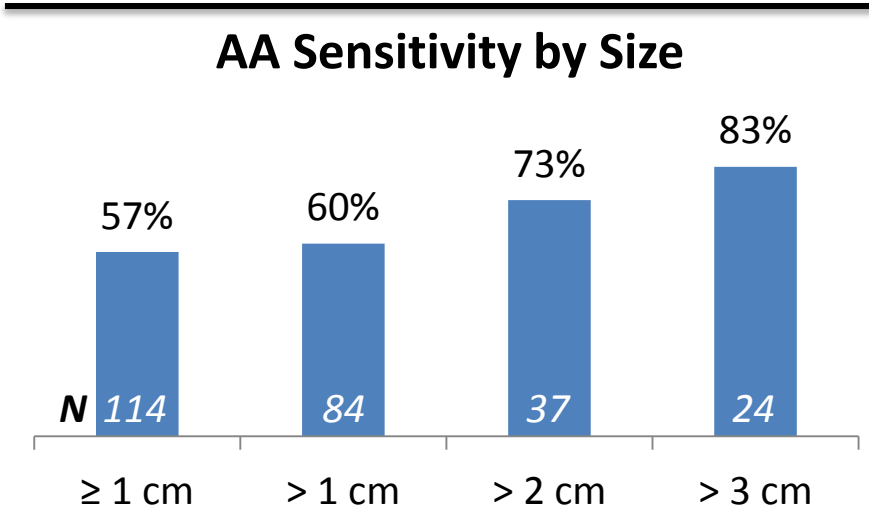
Algorithm Cut-off Study Design

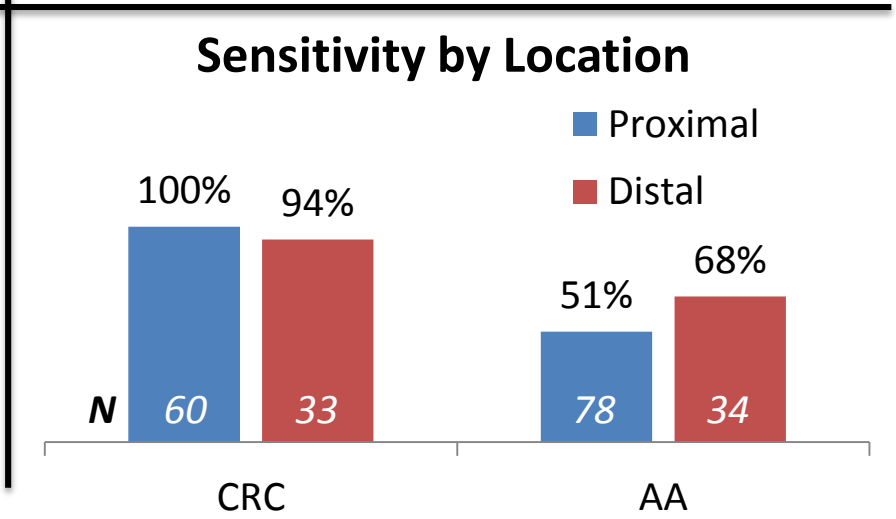
Objective	**Optimize algorithm** on sample population to maximize sensitivity while maintaining acceptable specificity level
Enrollment	**1,003 total subjects** ▪ 93 CRC cases ▪ 114 AA cases
Process	**1) Enroll subjects** ▪ Colonoscopy completed for every subject **2) Test stool markers** ▪ Measure value for all 11 markers **3) Optimize algorithm** ▪ Build logistic regression models ▪ Define logistic equation ▪ Set cut-off at nominal 90% specificity

Optimized Algorithm Results









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Analytical Testing Overview

- **Analytical testing met all protocol objectives**
- **Key types of testing:**
  - ***Reproducibility studies***
    - >98% agreement between laboratory testing sites
    - >98% agreement between different manufacturing lots
    - <20% CV across positive Cologuard scores
  - ***Interference studies***
    - No interference from various foods, pharmaceuticals, or other substances
  - ***Stability (time and temperature)***

DeeP-C Pivotal Study

Thomas F. Imperiale, M.D.

Professor of Medicine, Indiana University

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Study Design

DeeP-C Pivotal Study

Overview

Primary Objective

Determine sensitivity and specificity of Cologuard for CRC

Secondary Objective

Compare sensitivity and specificity of Cologuard to FIT for CRC and Advanced Adenoma

Prospective, multicenter study

- 90 Sites to enroll >10,000 subjects
- All subjects complete Cologuard, FIT, and colonoscopy (reference method)
- Designed with input from national experts, FDA, and CMS

Primary Endpoints

	Endpoint	Success Criteria
1	**CRC Sensitivity** Colonoscopy as reference method	**65%** One-sided 95% lower bound
2	**Specificity** Colonoscopy as reference method	**85%** One-sided 95% lower bound

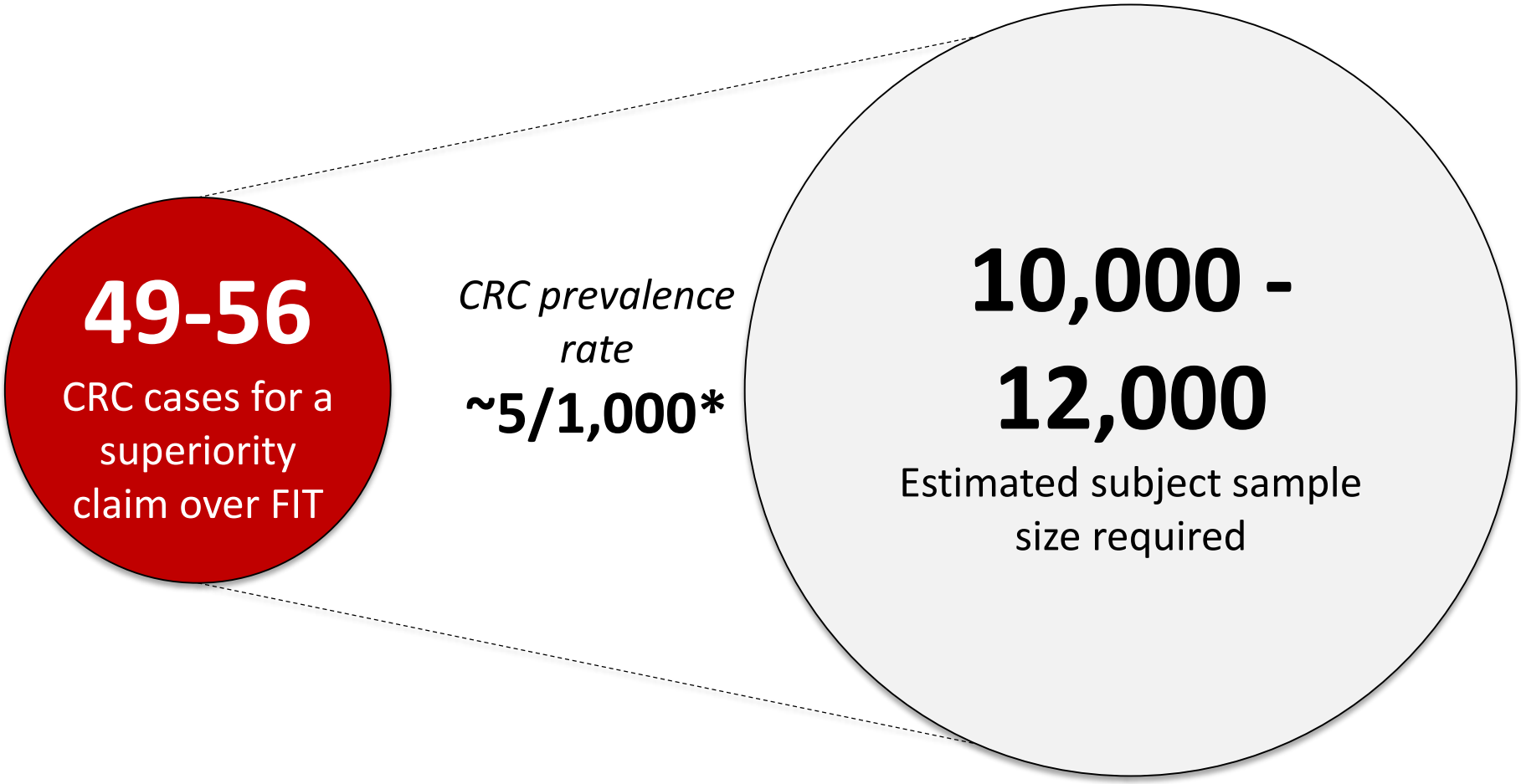
Secondary Endpoints

	Endpoint	Success Criteria
3	**CRC Sensitivity** Colonoscopy as reference method	**Non-inferiority to FIT** Performance difference no more than 5% (using 95% CI lower bound)
		Superiority to FIT McNemar's comparison test, one-sided p-value <0.025
4	**AA Sensitivity** Colonoscopy as reference method	**Superiority to FIT** McNemar's comparison test, one-sided p-value <0.025

Key Eligibility Criteria

- Adults between the ages of 50 and 84 years (inclusive)
- At *average risk* for CRC
  - No history of CRC or adenoma, aerodigestive tract cancer, or high risk conditions for CRC
  - No family history of FAP or HNPCC
  - No positive fecal occult blood test or FIT in the previous 6 months
  - No prior colorectal resection for any reason other than sigmoid diverticular disease
  - No overt rectal bleeding in the previous 30 days
- No colonoscopy in past 9 years or barium x-ray, virtual colonoscopy, or flexible sigmoidoscopy in the past 5 years

Sample Size Calculation



*Age enrichment used to increase incidence rate, however, study population still reflective of US screening population

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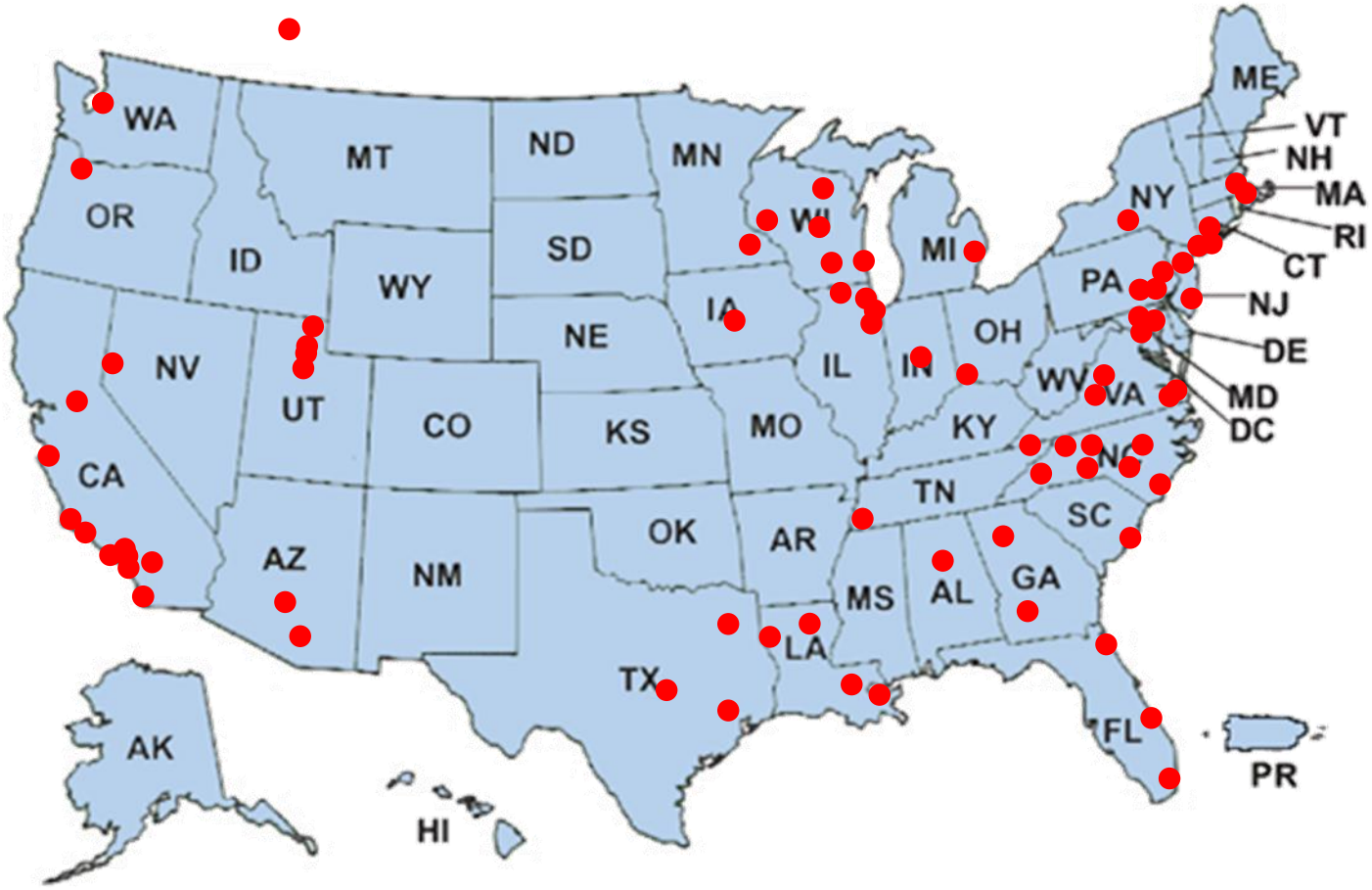
90 Enrollment Sites



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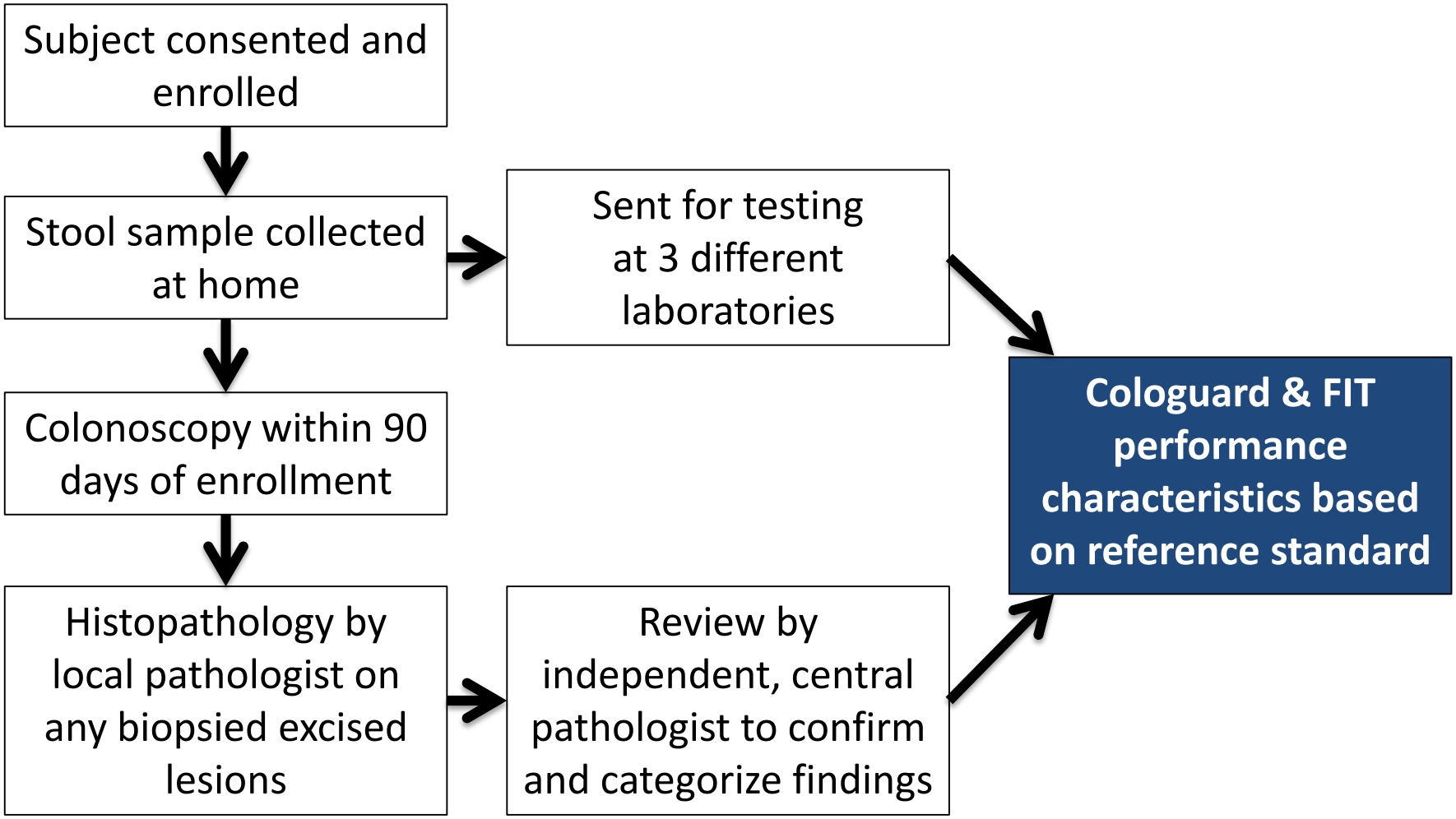
Study Procedures



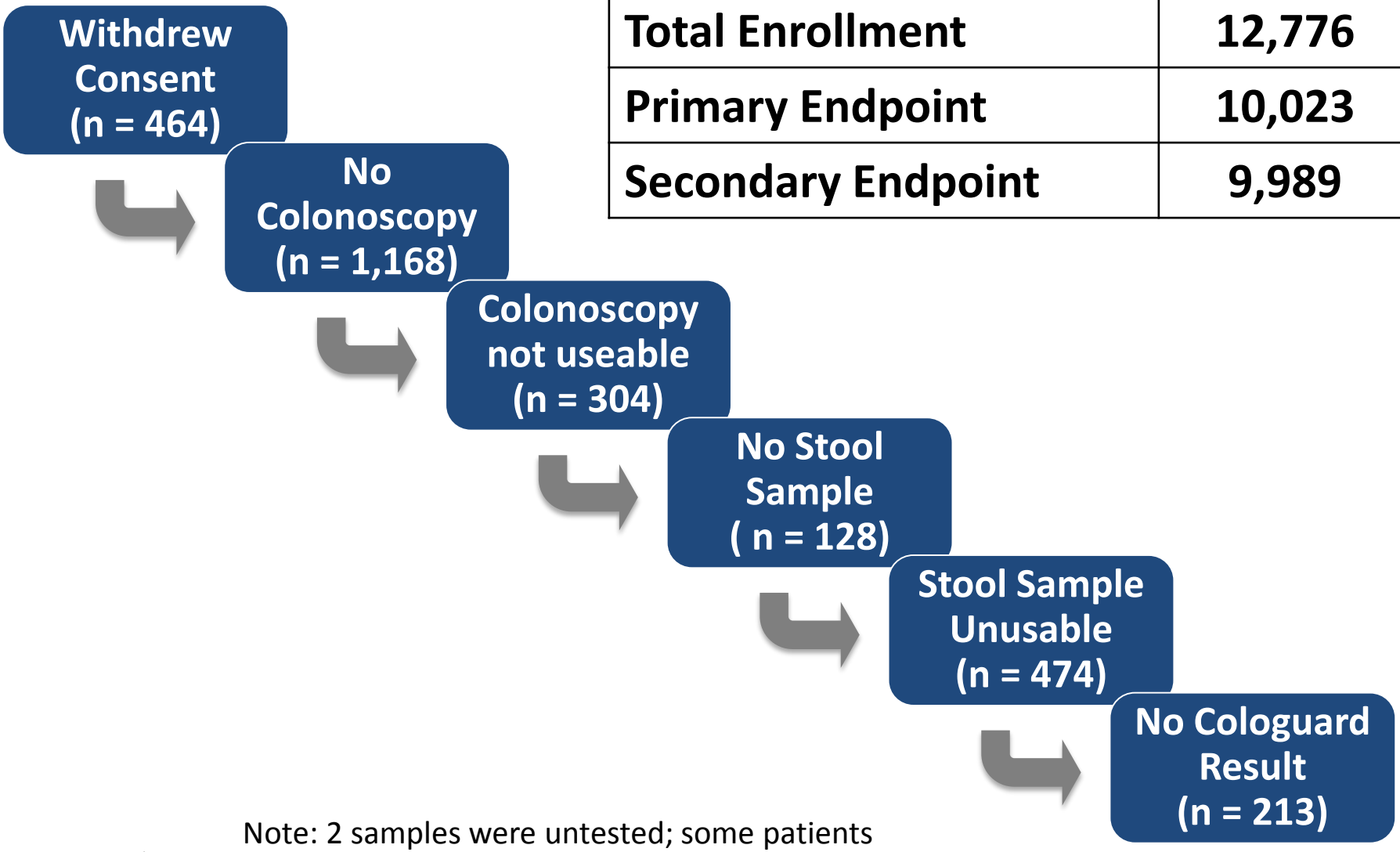
Categorization of Findings for Analysis

Category	Findings
1	**CRC, all stages**
2	**Advanced adenoma**
	2.1 Adenoma with high grade dysplasia, any size
	2.2 Adenoma with villous growth pattern (≥ 25%), any size
	2.3 Adenoma ≥ 1.0 cm in size
	2.4 Serrated lesion, ≥ 1.0 cm in size
3-5	**Non-advanced adenoma** (considered negative)
6	**Negative**

Enrollment & Study Population

DeeP-C Pivotal Study

DeeP-C Enrollment Overview



Total Enrollment	12,776
Primary Endpoint	10,023
Secondary Endpoint	9,989

Note: 2 samples were untested; some patients are missing data for multiple reasons

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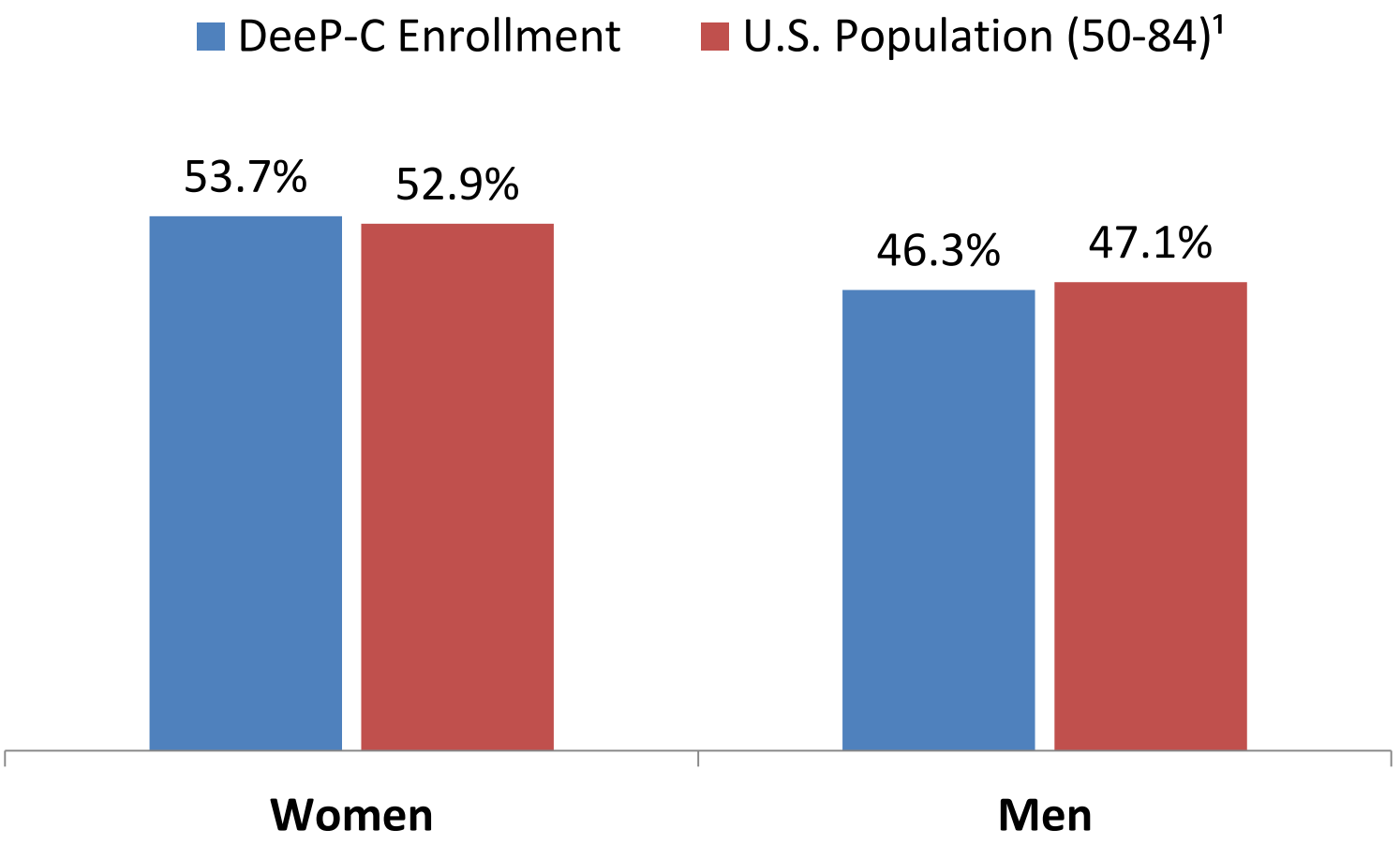
Enrollment by Sex

(Primary endpoint population – 10,023)

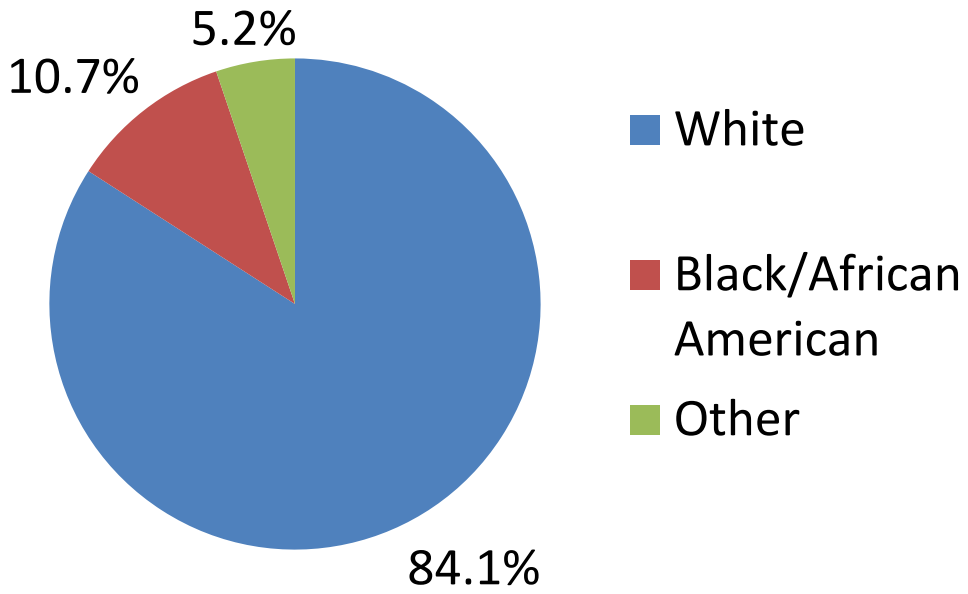


[1]US Census Bureau 2012 estimate

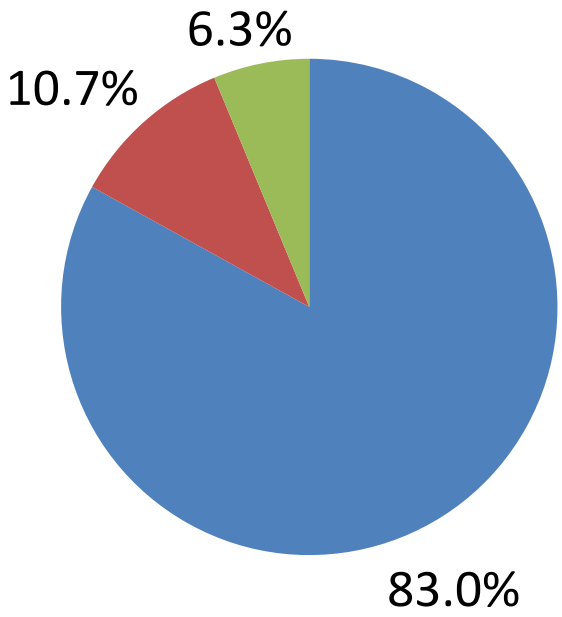
Enrollment by Race

(Primary endpoint population – 10,023)

DeeP-C Enrollment



US Population 50-84[1]

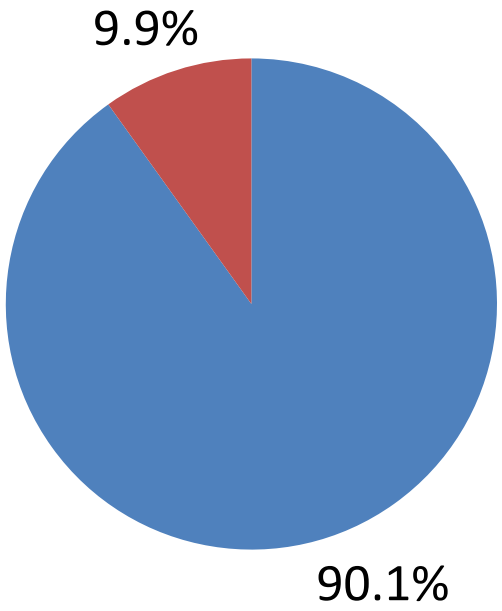


[1]US Census Bureau 2012 estimate

Enrollment by Ethnicity

(Primary endpoint population – 10,023)

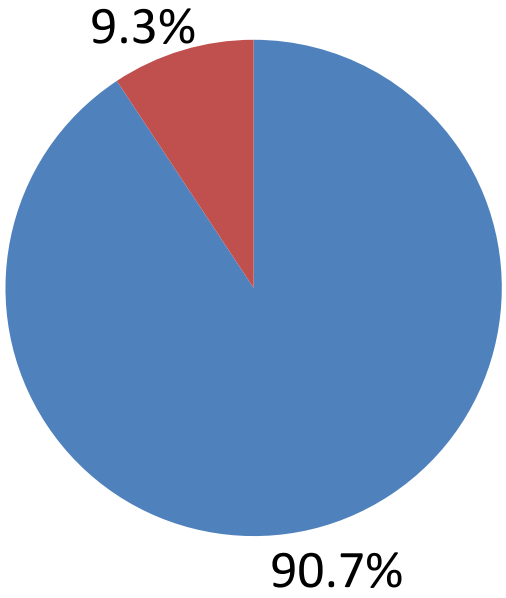
DeeP-C Enrollment



Not Hispanic

Hispanic

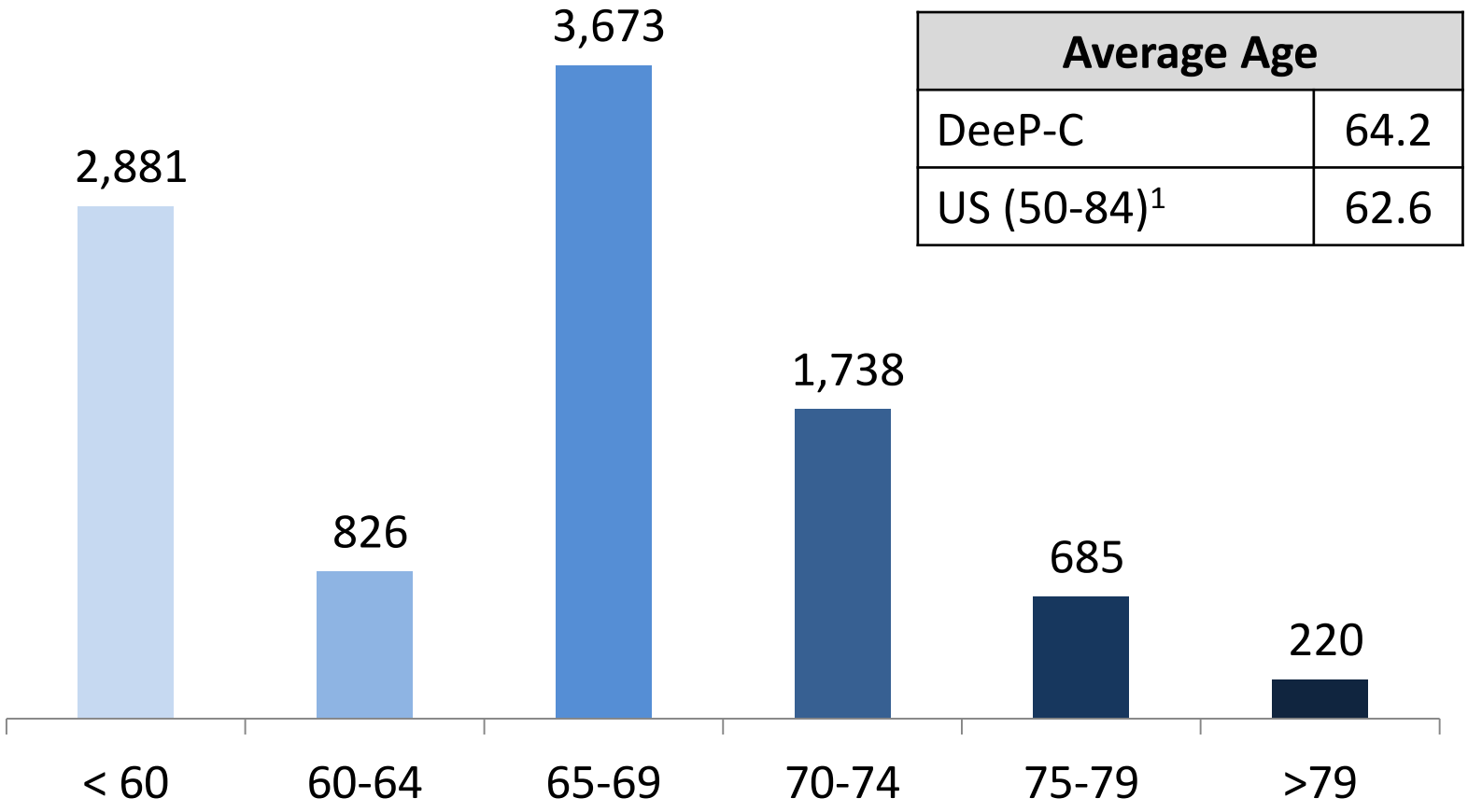
US Population 50-84[1]



[1]US Census Bureau 2012 estimate

Enrollment by Age

(Primary endpoint population – 10,023)

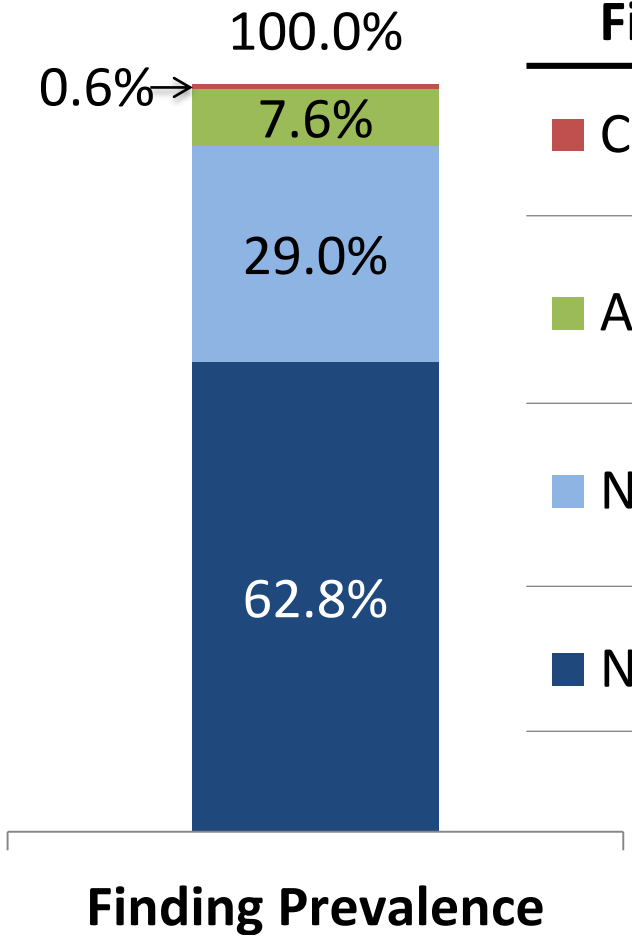


Average Age	
DeeP-C	64.2
US (50-84)[1]	62.6

[1]US Census Bureau 2012 estimate

DeeP-C Findings

(Primary endpoint population – 10,023)



Finding	Valid Cases
CRC	65
Advanced Adenoma	760
Non-advanced adenoma	2,903
Negative	6,295

Study Results

DeeP-C Pivotal Study

Overview

- Primary and secondary endpoints
- Statistical analysis and ROC curves
- Sub-analysis performance
  - Demographics
  - CRC stage and location
  - AA type, size and location

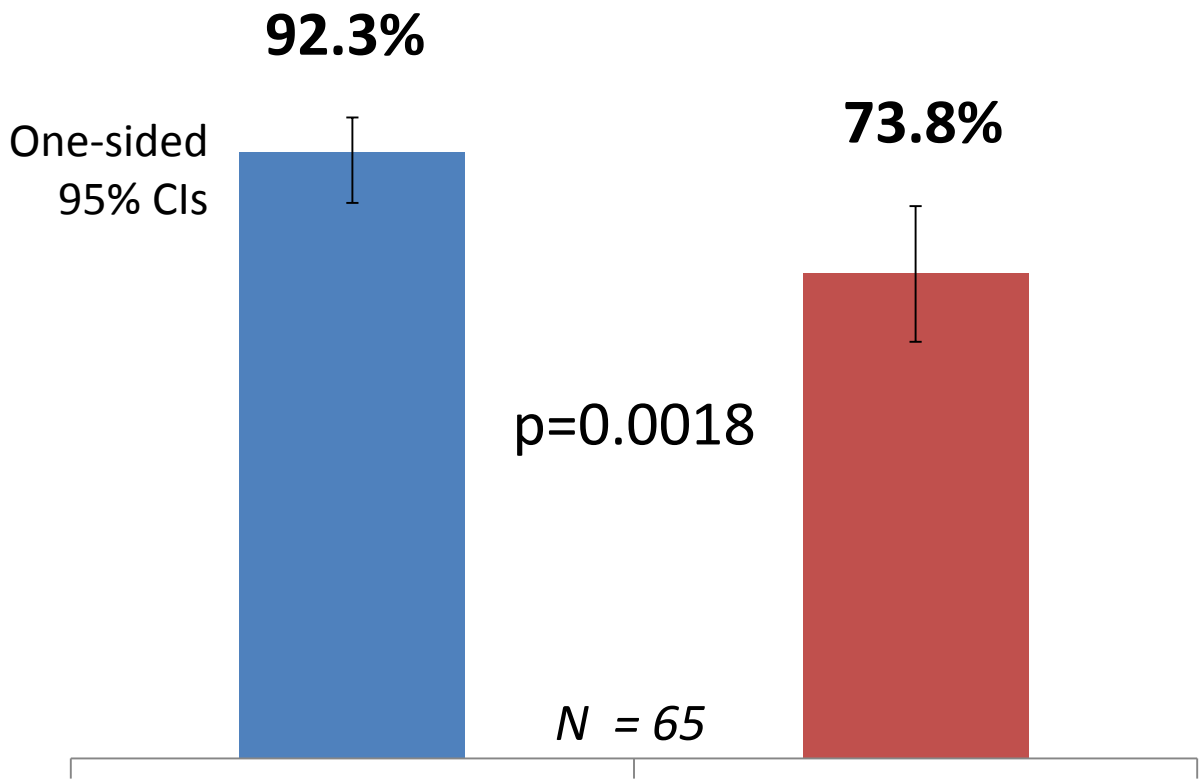
CRC Sensitivity

	Observed CRC Sensitivity	Two-sided 95% confidence interval	One-sided 95% lower bound CI
DeeP-C Results	**92.3%** (60/65)	**83.0% - 97.5%**	**84.5%**
Primary Endpoint			**65.0%**

Specificity

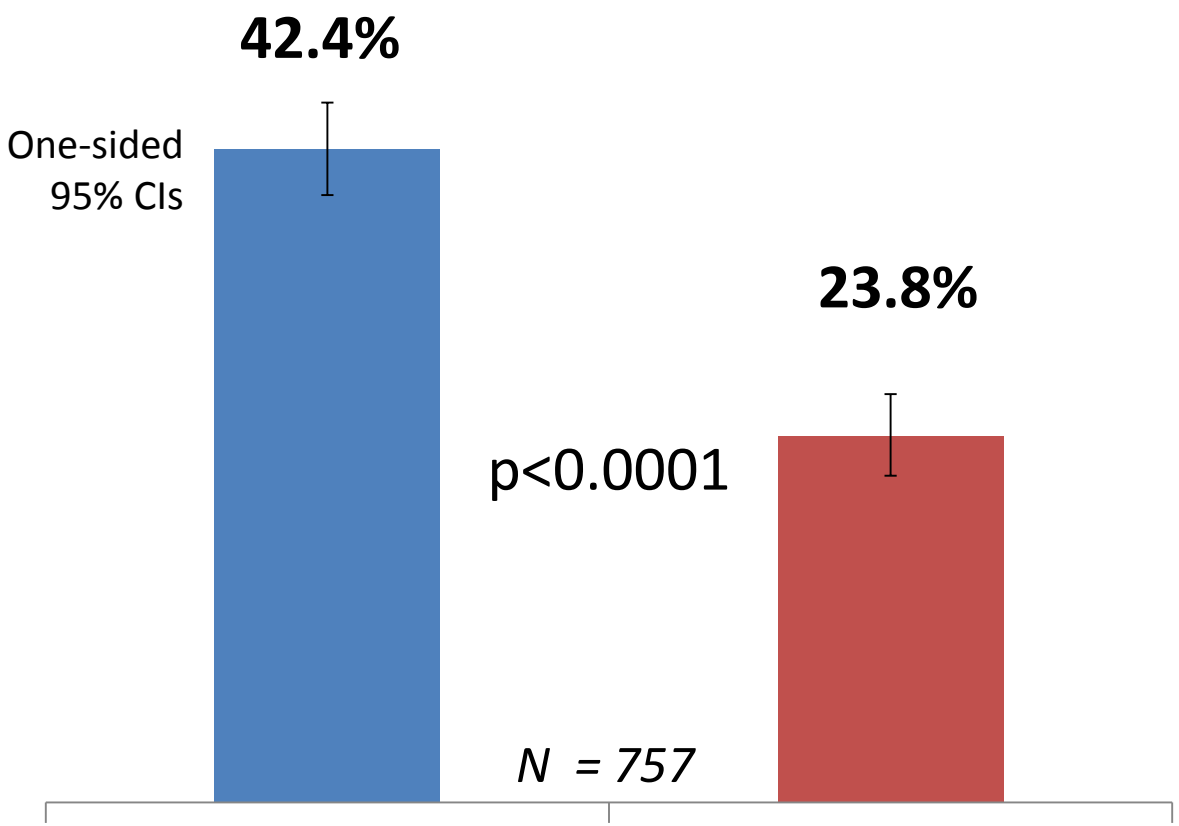
	Observed Specificity	Two-sided 95% confidence interval	One-sided 95% lower bound CI
DeeP-C Results	**86.6%** (7,967/9,198)	**85.9% - 87.2%**	**86.0%**
Primary Endpoint			**85.0%**

CRC Sensitivity: Cologuard vs. FIT



	Cologuard	FIT
Two-sided 95% CI	*83.0% - 97.5%*	*61.5% - 84.0%*

Advanced Adenoma Sensitivity: Cologuard vs. FIT



	Cologuard	FIT
Two-sided 95% CI	*38.9% - 46.0%*	*20.8% - 27.0%*

CRC Table

		Cologuard +	Cologuard –
FIT	+	47	**1****
FIT	–	**13***	4

P = 0.0018

*9 stage I, 4 stage II
**Stage I

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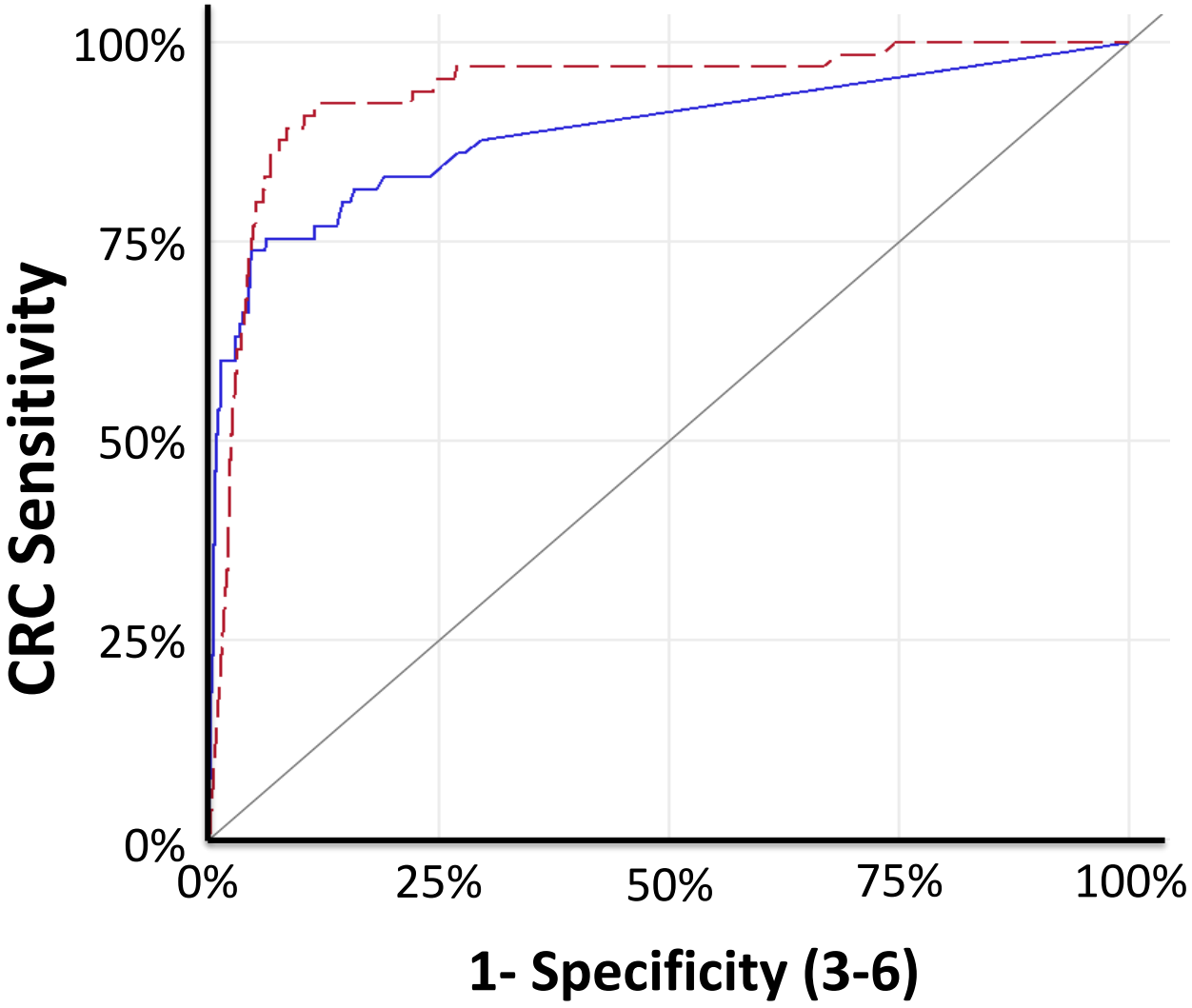
Advanced Adenoma Table

		Cologuard +	Cologuard –
FIT	+	151	**29**
FIT	–	**170**	407

P < 0.0001

ROC Curves
CRC Sensitivity vs. Specificity



Area Under the Curve	
Cologuard	=0.9393
FIT	=0.8871
P-value	=0.0372

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CRC and Advanced Adenoma Summary

	Cologuard Performance	FIT Performance	P-Value
Cancer	**92.3%** (60/65)	**73.8%** (48/65)	**0.0018**
Advanced Adenoma	**42.4%** (321/757)	**23.8%** (180/757)	**< 0.0001**

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CRC Sensitivity by Demographics

		Cologuard	FIT	% Point Difference
Sex	Men (N=34)	100.0%	79.4%	20.6%
	Women (N=31)	83.9%	67.7%	16.1%
Race & Ethnicity	White (N=55)	96.4%	78.2%	18.2%
	Black/African American (N=8)	62.5%	50.0%	12.5%
	Hispanic/Latino (N=9)	88.9%	77.8%	11.1%
Age (Years)	< 60 (N=7)	100.0%	85.7%	14.3%
	60 – 64 (N=4)	75.0%	50.0%	25.0%
	65 – 69 (N=20)	95.0%	75.0%	20.0%
	70 – 74 (N=18)	88.9%	77.8%	11.1%
	75 – 79 (N=6)	100.0%	83.3%	16.7%
	> 79 (N=10)	90.0%	60.0%	30.0%

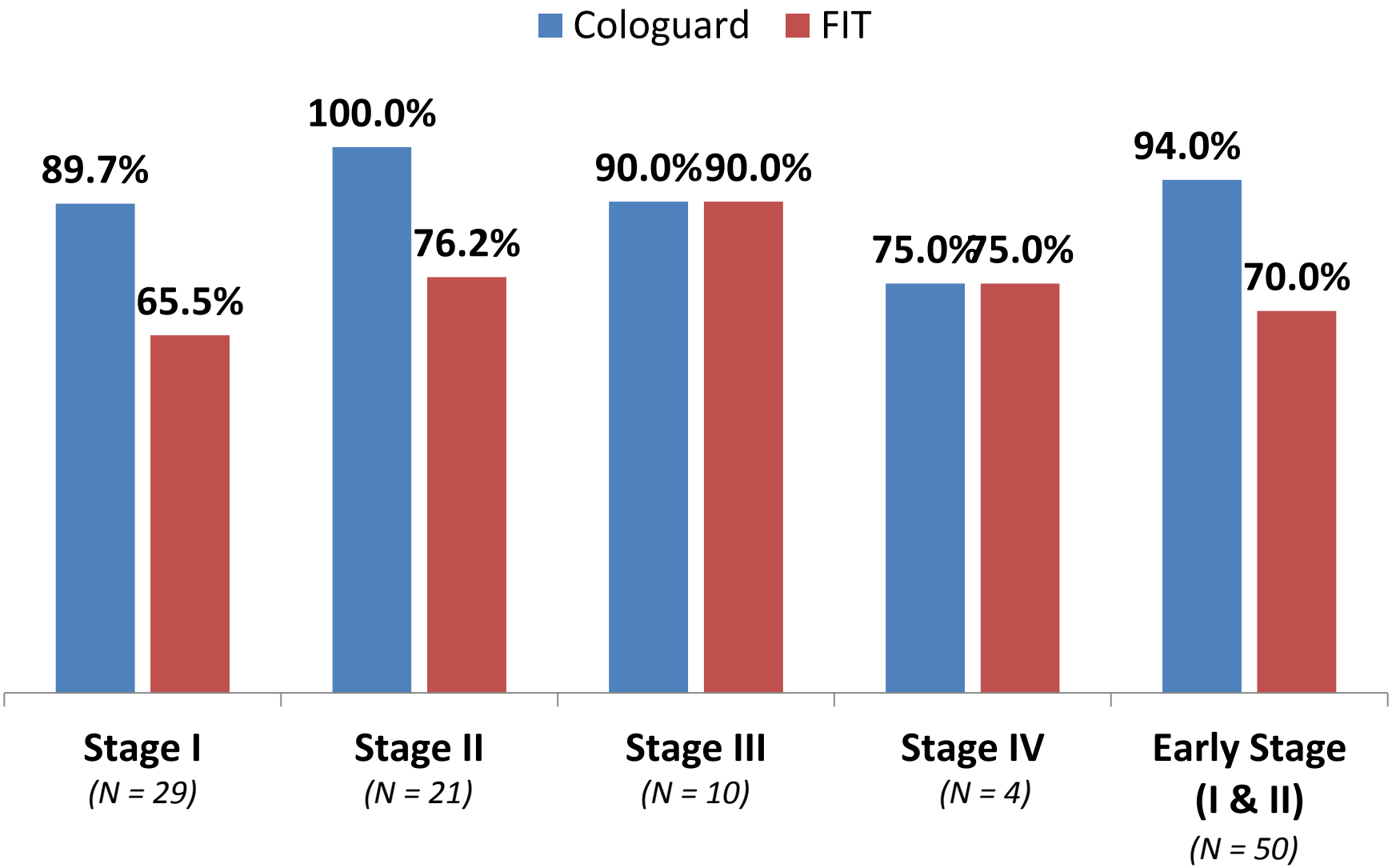
Advanced Adenoma Sensitivity by Demographics

		Cologuard	FIT	% Point Difference
Sex	Men (N=447)	44.7%	26.8%	17.9%
	Women (N=310)	39.0%	19.4%	19.7%
Race & Ethnicity	White (N=638)	42.3%	22.7%	19.6%
	Black/African American (N=85)	42.4%	30.6%	11.8%
	Hispanic/Latino (N=59)	39.0%	23.7%	15.3%
Age (Years)	< 60 (N=168)	38.1%	23.8%	14.3%
	60 – 64 (N=57)	42.1%	26.3%	15.8%
	65 – 69 (N=301)	41.5%	23.6%	17.9%
	70 – 74 (N=154)	46.8%	23.4%	23.4%
	75 – 79 (N=62)	46.8%	17.7%	29.1%
	> 79 (N=15)	46.7%	46.7%	0.0%

Specificity by Demographics

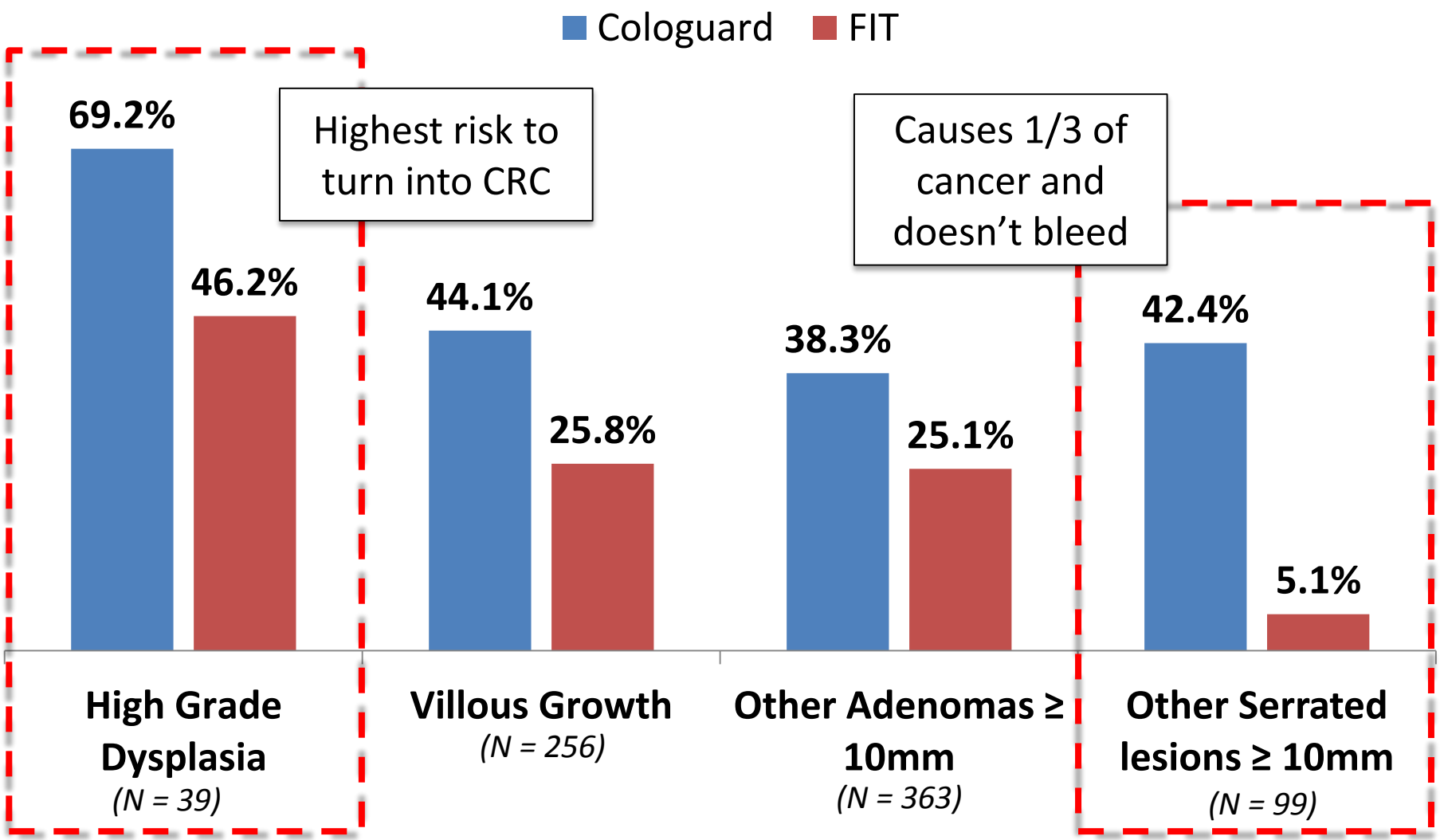
		Cologuard
Sex	Men (N=4,161)	85.8%
	Women (N=5,037)	87.3%
Race & Ethnicity	White (N=7,726)	85.9%
	Black/African American (N=879)	89.9%
	Hispanic/Latino (N=923)	90.7%
Age (Years)	< 60 (N=2,703)	92.2%
	60 – 64 (N=765)	89.0%
	65 – 69 (N=3,352)	85.7%
	70 – 74 (N=1,566)	82.5%
	75 – 79 (N=617)	77.8%
	> 79 (N=195)	77.9%

CRC Sensitivity by Cancer Stage



Note: Stage unavailable for one cancer

Advanced Adenoma Sensitivity by Type



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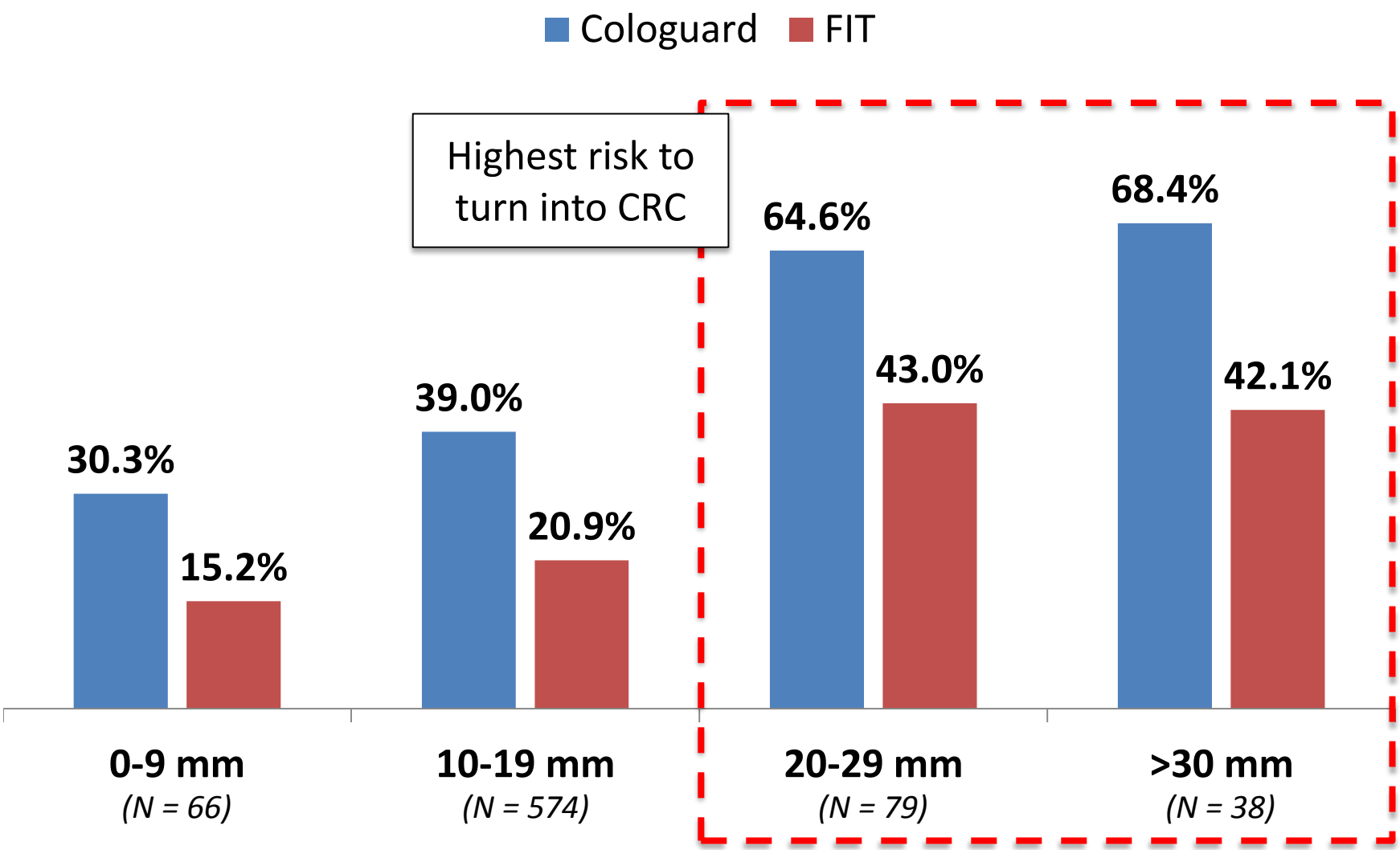
Advanced Adenoma Sensitivity by Size



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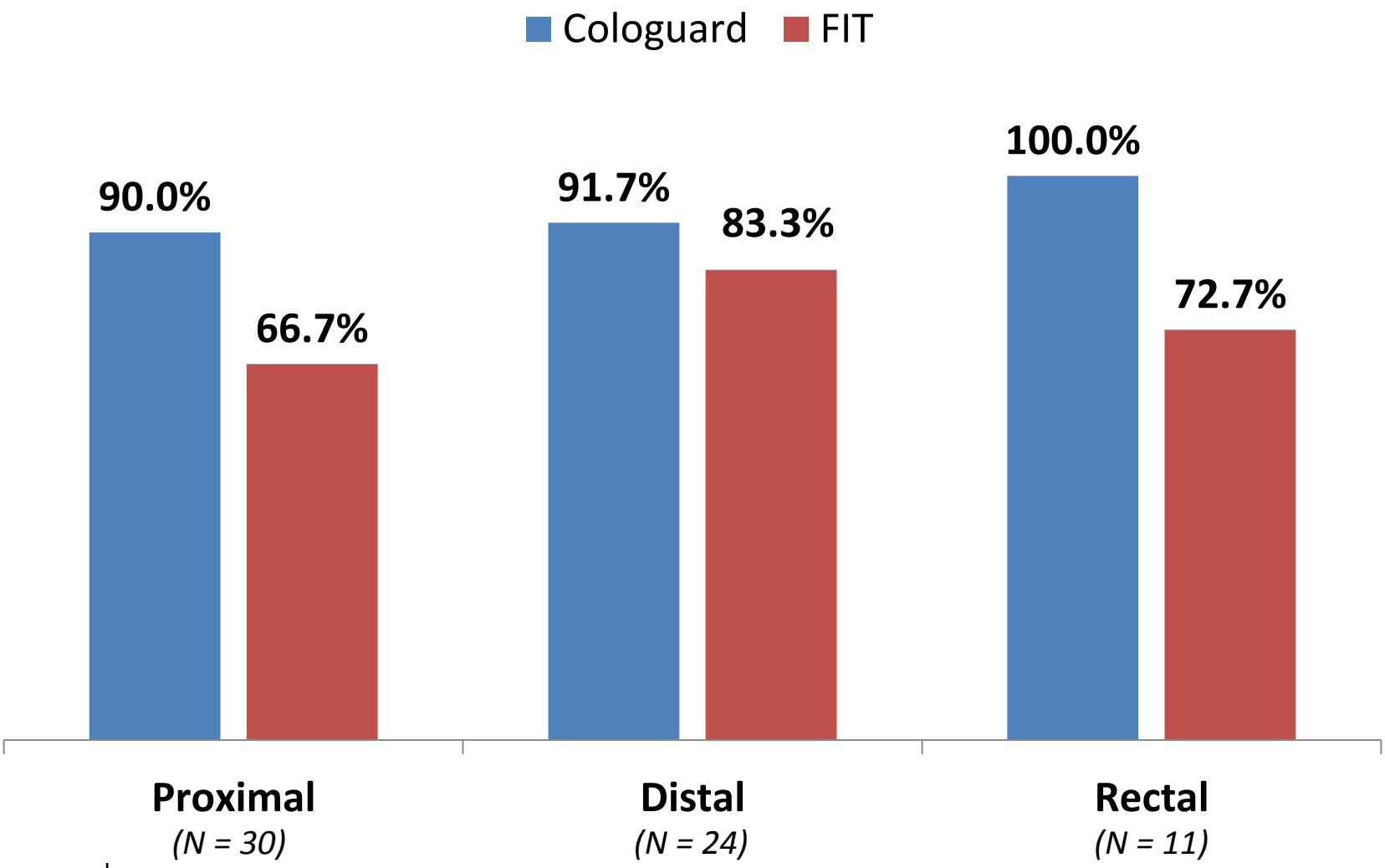
CRC Sensitivity by Location



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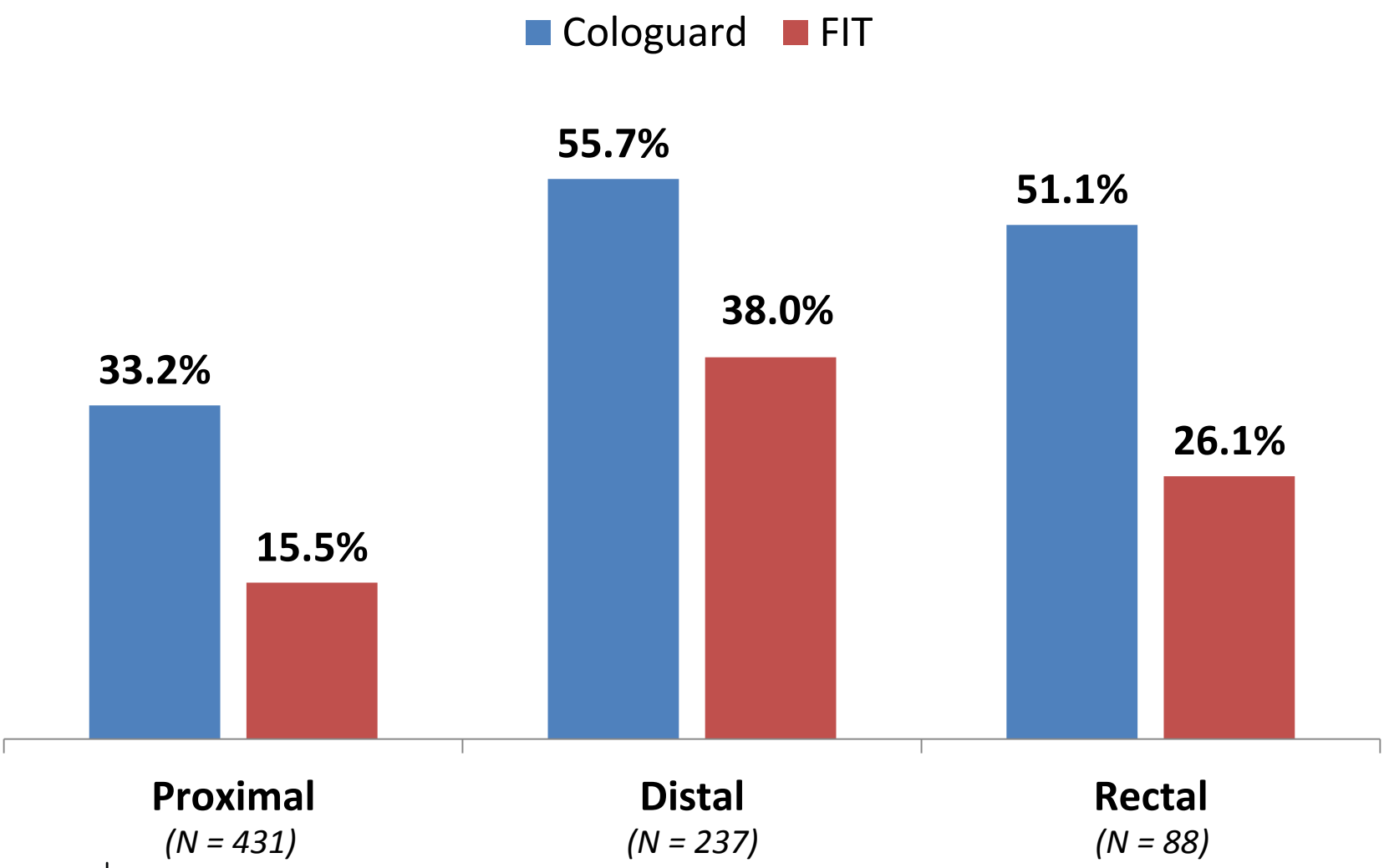
Advanced Adenoma Sensitivity by Location



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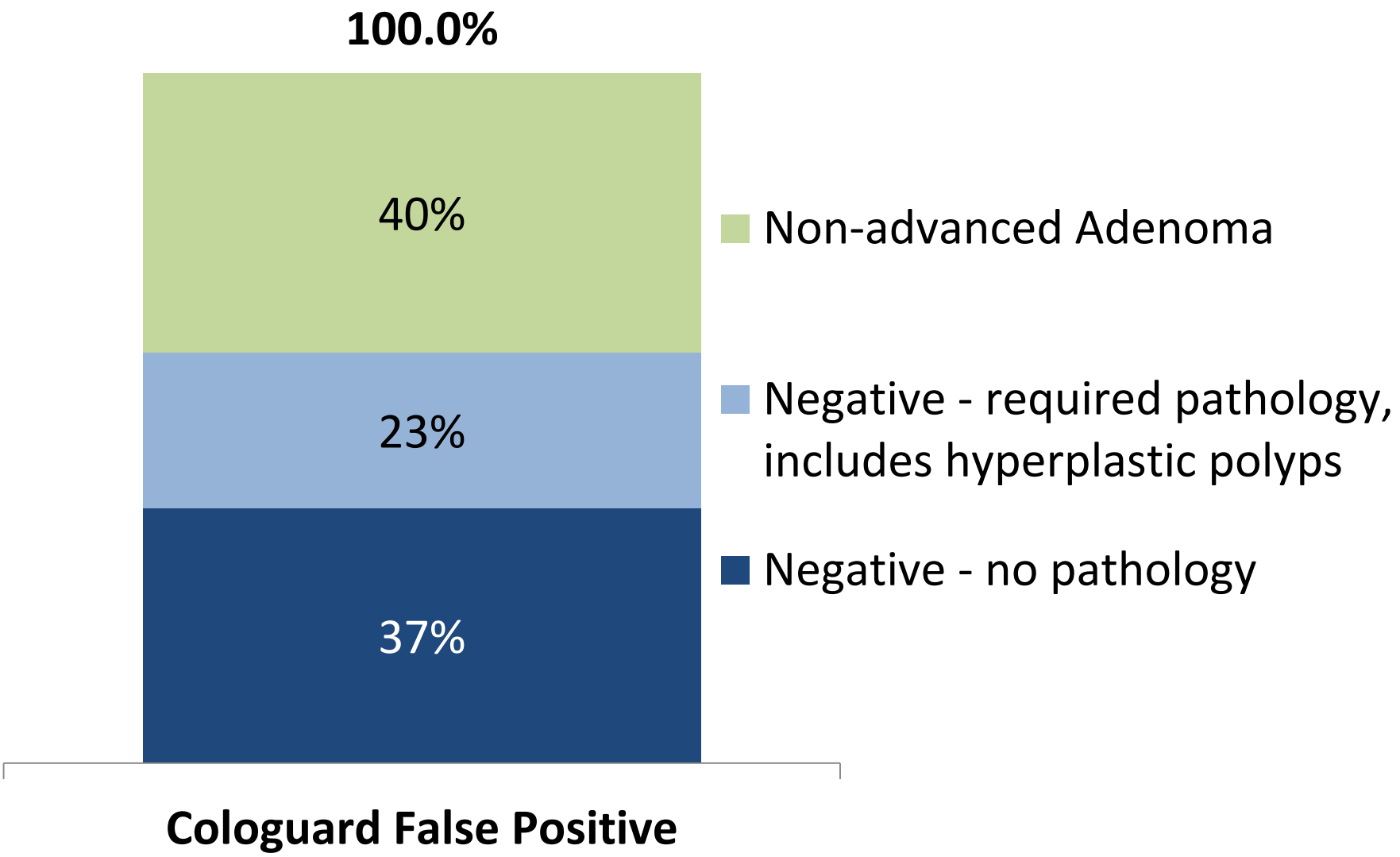
Specificity by Negative Category

Category	Finding	Specificity
3	1-2 Adenomas 5-<10 mm	607/749 (81.0%)
4	≥3 Adenomas <10 mm, Non-advanced	302/419 (72.1%)
5	1-2 Adenomas ≤5 mm, Non-advanced	1,496/1,735 (86.2%)
6.1	Negative upon histopathological review (includes hyperplastic polyps)	1,543/1,821 (84.7%)
6.2	No findings on colonoscopy, no histopathological review	4,019/4,474 (89.8%)

False Positive Distribution



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Summary of Endpoints

	Endpoint	DeeP-C Result
1	**65% lower bound CRC sensitivity**	✓ ▪ 92.3% CRC sensitivity ▪ 84.5% one-sided 95% CI
2	**85% lower bound specificity**	✓ ▪ 86.6% specificity ▪ 86.0% one-sided 95% CI
3	**Non-inferiority to FIT for CRC sensitivity**	✓ ▪ 92.3% CRC sensitivity (FIT = 73.8%)
	Superiority to FIT for CRC sensitivity	✓ ▪ p=0.0018
4	**Superiority to FIT for AA sensitivity**	✓ ▪ 42.4% AA sensitivity (FIT = 23.8%) ▪ p <0.0001

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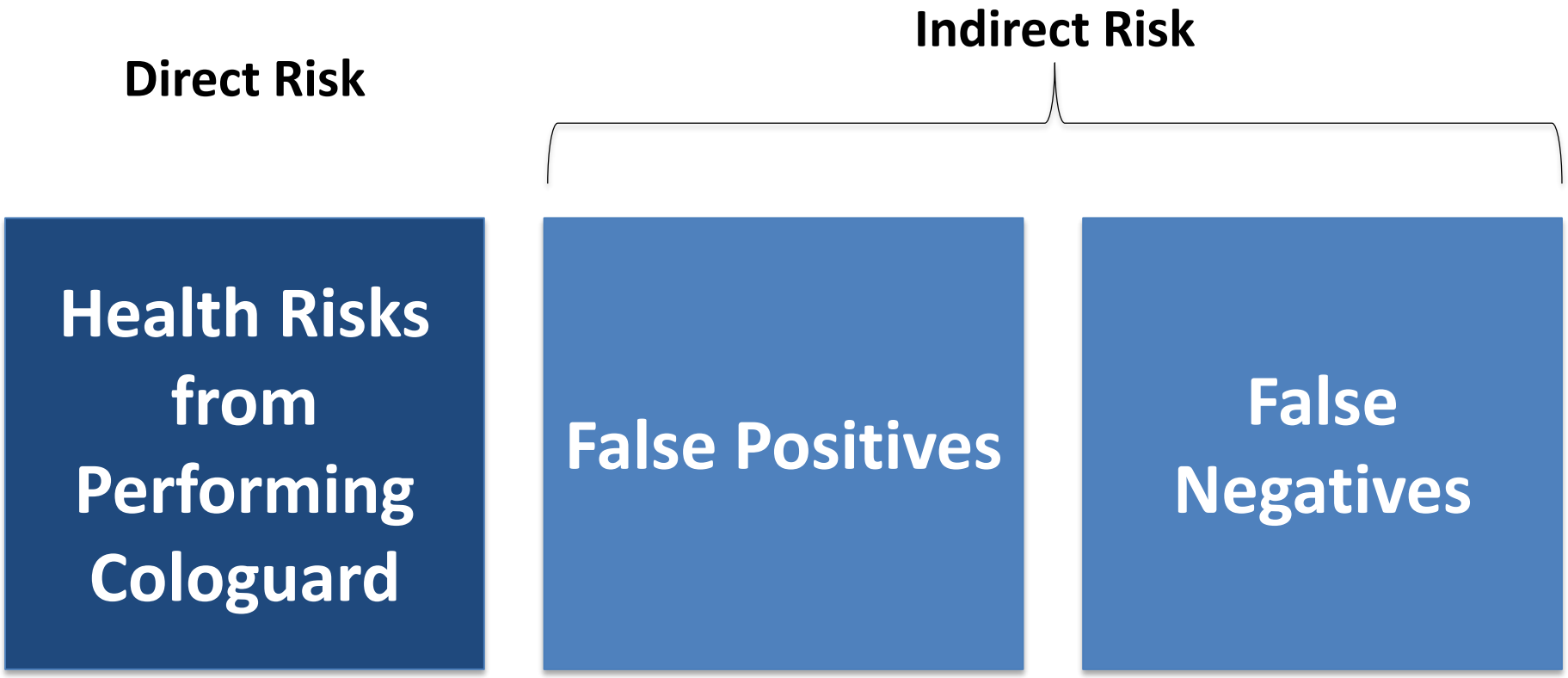
Number Needed to Screen per Finding
(95% CI)

	Colonoscopy	Cologuard	FIT
Any colorectal cancer	**154** (120-200)	**166** (130-217)	**208** (156-286)
Stage I to III colorectal cancer	**166** (130-217)	**178** (140-238)	**227** (169-313)
Advanced precancerous lesion	**13** (12-14)	**31** (28-35)	**55** (48-65)

Safety of Cologuard

Cologuard Risks



Cologuard Direct Risks

- ***Low direct risk to patient health***
  - Non-invasive test
  - No bowel preparation or dietary restrictions
  - Collection kit allows stool to be collected during normal bowel movement in toilet
- ***DeeP-C Adverse Events***
  - Adverse events limited to stool collection process
  - No reported Serious Adverse Events (SAEs)
    - All reported events (n=4) were “mild”
  - One subject died prior to undergoing colonoscopy, due to narcotic and ethanol intoxication
    - Was deemed unrelated to the study

False Positive Risk: Hypothetical Screening of 100,000 People

	Screening Colonoscopy	Cologuard	FIT
CRC	700	647	518
AA	7,580	3,216	1,803
'Negatives'	91,720	12,316*	4,722*
Serious Adverse Events** from Colonoscopy[1]	680	110	48
Serious Adverse Events per CRC & AA Detected	0.082	0.028	0.021

*False positive results

**6.8 serious complications/1,000 colonoscopies

[1]Rutter, et. al., Cancer Causes Control (2012)

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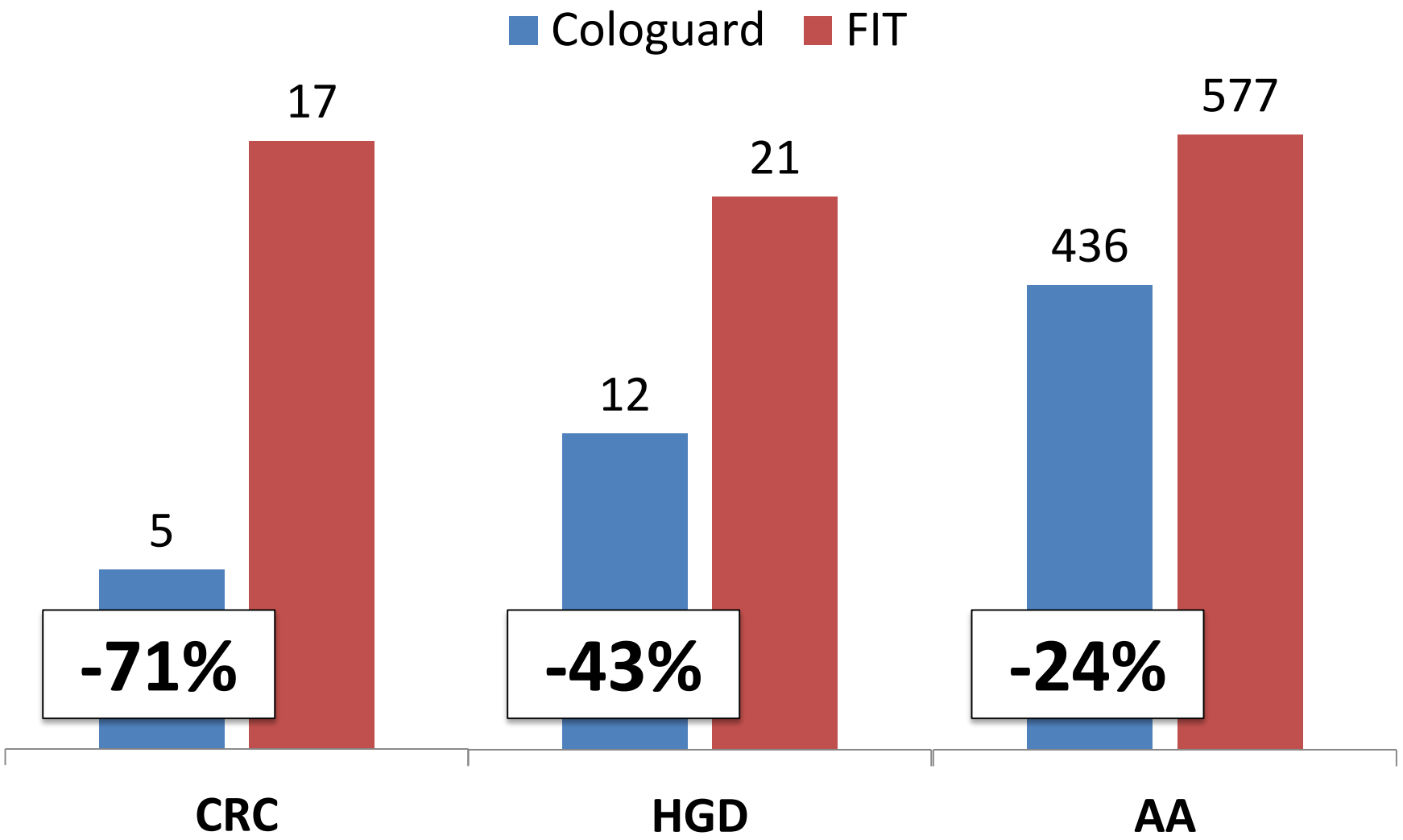
False Negatives in DeeP-C



Cologuard Benefits

- High sensitivity for early stage CRC
- Cancer detection throughout the colon
- Improved advanced adenoma detection
- Balance specificity with sensitivity
- Safe and simple to use

Cologuard Benefits

High sensitivity for early stage CRC

- 92.3% overall cancer sensitivity
- Demonstrated superiority compared to FIT
- 94.0% Stage I-II sensitivity (vs. 70.0% for FIT)

Cancer detection throughout the colon

Improved advanced adenoma detection

Balance specificity with sensitivity

Safe and simple to use

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Cologuard Benefits

High sensitivity for early stage CRC

Cancer detection throughout the colon

- 90.0% CRC sensitivity in proximal colon (vs. 66.7% FIT)
- 91.7% CRC sensitivity in distal colon (vs. 83.3% FIT)
- 100% CRC sensitivity in rectum (vs. 72.7% FIT)

Improved advanced adenoma detection

Balance specificity with sensitivity

Safe and simple to use

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Cologuard Benefits

High sensitivity for early stage CRC

Cancer detection throughout the colon

Improved advanced adenoma detection

- Demonstrated superiority compared to FIT
- 69.2% sensitivity for high grade dysplasia
- 42.4% sensitivity for sessile serrated (vs. 5.1% for FIT)

Balance specificity with sensitivity

Safe and simple to use

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Cologuard Benefits

High sensitivity for early stage CRC

Cancer detection throughout the colon

Improved advanced adenoma detection

Balance specificity with sensitivity

- 86.6% specificity, met primary endpoint
- 89.8% clean colon specificity (category 6.2)

Safe and simple to use

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Cologuard Benefits

High sensitivity for early stage CRC

Cancer detection throughout the colon

Improved advanced adenoma detection

Balance specificity with sensitivity

Safe and simple to use

- No serious adverse events in DeeP-C
- Take home sample collection device

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Risk/Benefit Balance

Benefits	Risks
High sensitivity for early stage CRC	False positives
Cancer detection throughout the colon	False negatives
Improved advanced adenoma detection	
Balance specificity with sensitivity	
Safe and simple to use	

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Post-Approval Study

Sandra Statz
VP of Clinical, Quality & Regulatory, Exact Sciences

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CC - 98

Proposed Study Design

Objective	To assess Cologuard performance at baseline and at 3 years in subjects at average risk for developing CRC.
Type	Prospective, longitudinal, multi-center study
Population	▪ Men and women between the ages of 50 and 84, inclusive ▪ Average risk of developing CRC
Sample Size	▪ 1,830 subjects ▪ 20 or more sites

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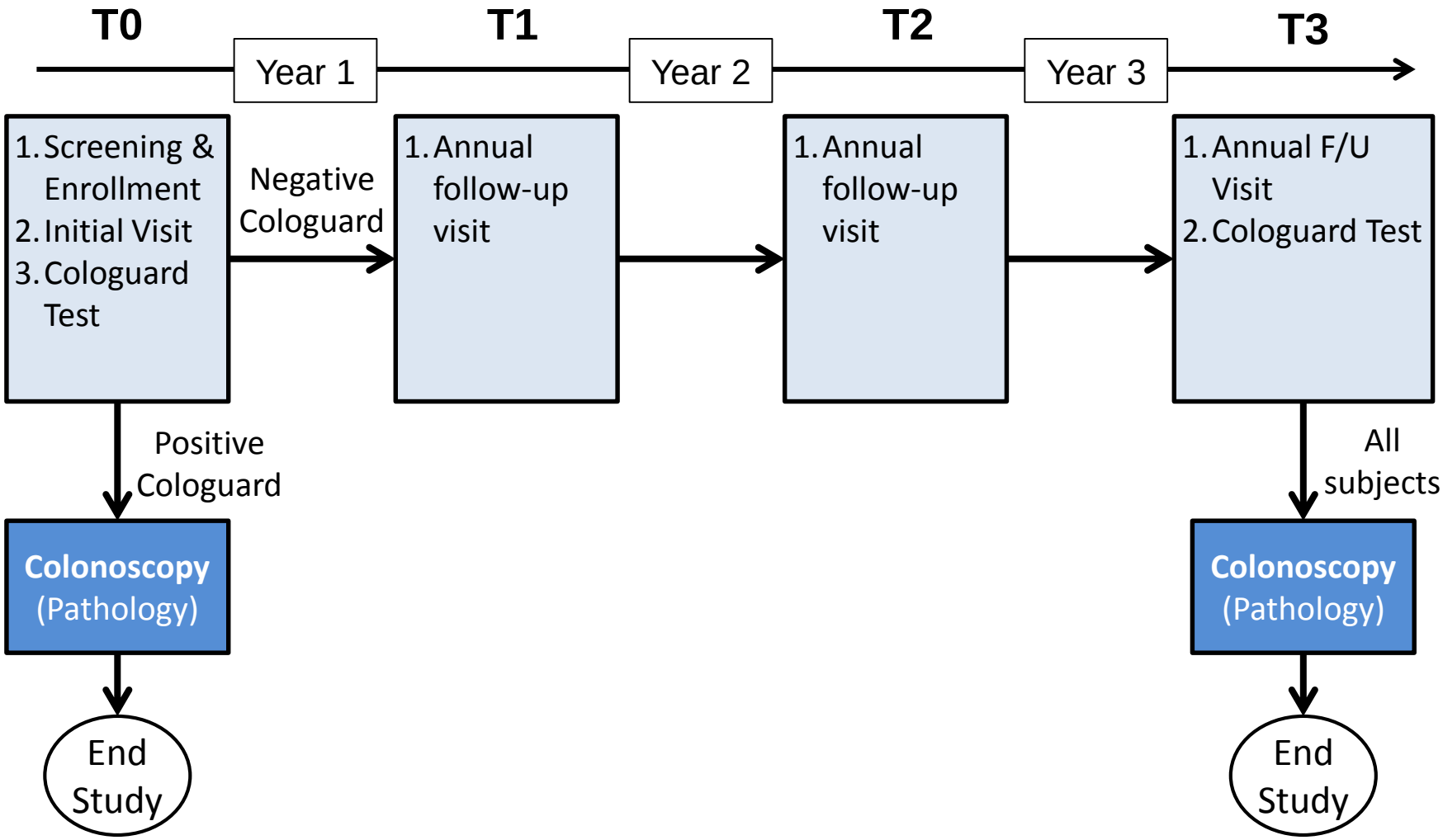
Study Subject Flow



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CC - 100

PAS Endpoints

- **Primary endpoint:**
  - Risk of CRC/AA among those with a positive Cologuard test at 3 years (T3) compared to baseline
- **Secondary endpoints:**
  - Distribution of colorectal epithelial lesions among positive Cologuard subjects at T0 and T3
  - Predictive values of a positive Cologuard at T0 and T3
- **Other outcomes**
  - Rate of no Cologuard result (e.g. invalid result)
  - Adverse event rate

PAS Rationale

- **Assessing safety & effectiveness at 3 years**
  - The T3 PPV can evaluate effectiveness at 3 years
    - Lower PPV at T3 could indicate that Cologuard lowers CRC/AA prevalence
    - Higher PPV at T3 suggests more frequent Cologuard testing may be beneficial
  - Allows for preliminary assessment of potential interval
  - Increased knowledge of performance over time will help justify future longitudinal studies with a three year interval
- **Interval modeling support**
  - The PAS is not designed to be a definitive study to establish interval, but could contribute inputs for interval modeling, such as positivity rates on repeat screening

Clinical Benefit

Sidney J. Winawer, M.D.

Paul Sherlock Chair

Memorial Sloan Kettering Cancer Center

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USPSTF CRC Screening Recommendation[1]

The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary.

2008 Grade A Recommendation

[1]Zauber, et al., Annals of Internal Medicine (2008)

Screening Options in Guidelines

Menu of Options*

- US Preventive Services Task Force[1]
- US Multi-society Task Force[2]
- American Cancer Society[3]
- European Union[4]

Colonoscopy Preferred

- American College of Gastroenterology[5]

***Options vary, but include:**

- FIT
- gFOBT
- Colonoscopy
- Flex. Sig.
- CT colo.
- Stool DNA
- DCBE

[1]USPSTF, Annals of Internal Medicine (2008)
[2]Levin, et. al., Gastroenterology (2008)
[3]ACS Website (2013)
[4]European Commission (2012)
[5]Rex, et. al., Am. J. Gastro. (2009)

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Guideline Development[1,2,3,4]

- Limited data available
- Long natural history of adenoma-cancer progression
- Expert opinion
- Modeling (ACS, USMSTF, USPSTF)
- Guidelines evolve with new data

[1]Winawer et. al., Gastroenterology (1997 & 2003)
[2]Levin, et. al., Gastroenterology (2008)
[3]USPSTF, Annals of Internal Medicine (2002 & 2008)
[4]Lieberman, et. al., Gastroenterology (2012)

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Evolution of Guidelines

	Introduced	Early Studies	Guideline Intervals	Definitive Studies
Sigmoidoscopy	1948	Hertz (1960)[1] Gilbertsen (1974)[2]	1980	2010-13
gFOBT	1967	Greegor (1967)[3]	1980	1993-96
Colonoscopy	1970	NPS (1993)[4] Selby (1992)[5]	1997	Ongoing - 2020's

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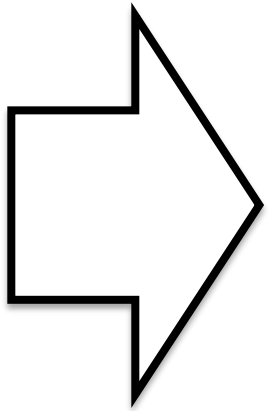
[1]Hertz, et. al, Postgrad Med (1960)
[2]Gilbertsen, Cancer (1974)
[3]Greegor, JAMA (1967)
[4]Winawer et. al., New Eng J Med (1993)
[5]Selby et. al., New Eng J Med (1992)

Paradigm Shift in CRC Screening

Early Stage Detection of CRC



Early Stage Detection of CRC

And

Detection and Removal of AA for prevention of CRC[1,2]

[1]Winawer et. al., New Eng J Med (1993)
[2]Zauber et al., NEJM, 2012

Limitations of FOBT for Screening[1,2]

Low sensitivity for early stage CRC and low sensitivity for advanced adenomas

Need for program of annual testing

Poor adherence to annual testing

[1]Levin, et. al., Gastroenterology (2008)
[2]USPSTF, Annals of Internal Medicine (2008)

Cologuard: A New Non-invasive Option

		Sensitivity		Specificity
		CRC	AA	
Invasive Tests	Colonoscopy[1]	95%	95%	90%
	Sigmoidoscopy[1]	~50% (95% distal only)	~50% (95% distal only)	92%
	CT Colonography	96%[2]	94%[3]	86%[4]-96%[3]
Non-Invasive Tests	**Cologuard[5]**	**92%**	**42%**	**87%**
	FIT[1]	**70%**	**22%**	**95%**
	gFOBT (Hemoccult SENSA) [1]	70%	24%	93%
	gFOBT (Hemoccult II) [1]	40%	12%	98%

[1]Zauber, et al., AHRQ (2009)
[2]Pickhardt et. al., Radiology (2011)
[3]Pickhardt et. al., NEJM (2003)
[4]Johnson, et. al., NEJM (2008)
[5]DeeP-C clinical study

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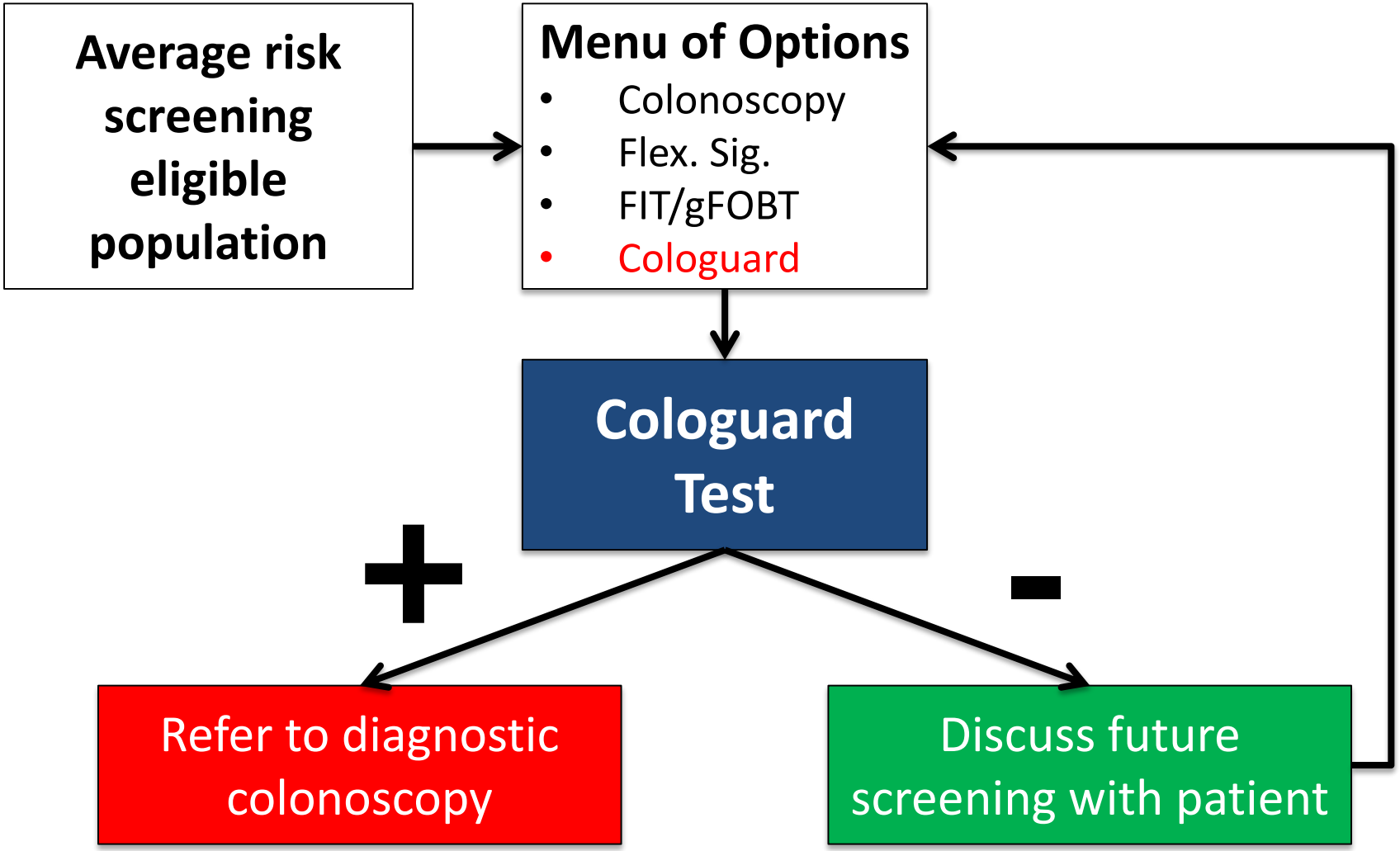
Clinical Use of Cologuard



Potential Clinical Benefits of Cologuard

Adds to the menu of screening options	▪ *Guidelines recommend offering patients the choice of both invasive and non-invasive screening modalities* ▪ *Cologuard would provide a new non-invasive option with a different performance profile*
Higher sensitivity than current non-invasive tests	▪ *Important for initial screening to be high sensitivity given imperfect adherence to programmatic screening programs* ▪ *Cologuard demonstrated significantly higher sensitivity than FIT, the leading non-invasive test*
Addresses the new CRC screening paradigm	▪ *Screening goal: reduce mortality by detecting early stage cancer and reducing cancer incidence by detecting and removing pre-cancer.* ▪ *Cologuard has high early-stage cancer sensitivity and clinically meaningful pre-cancer sensitivity*

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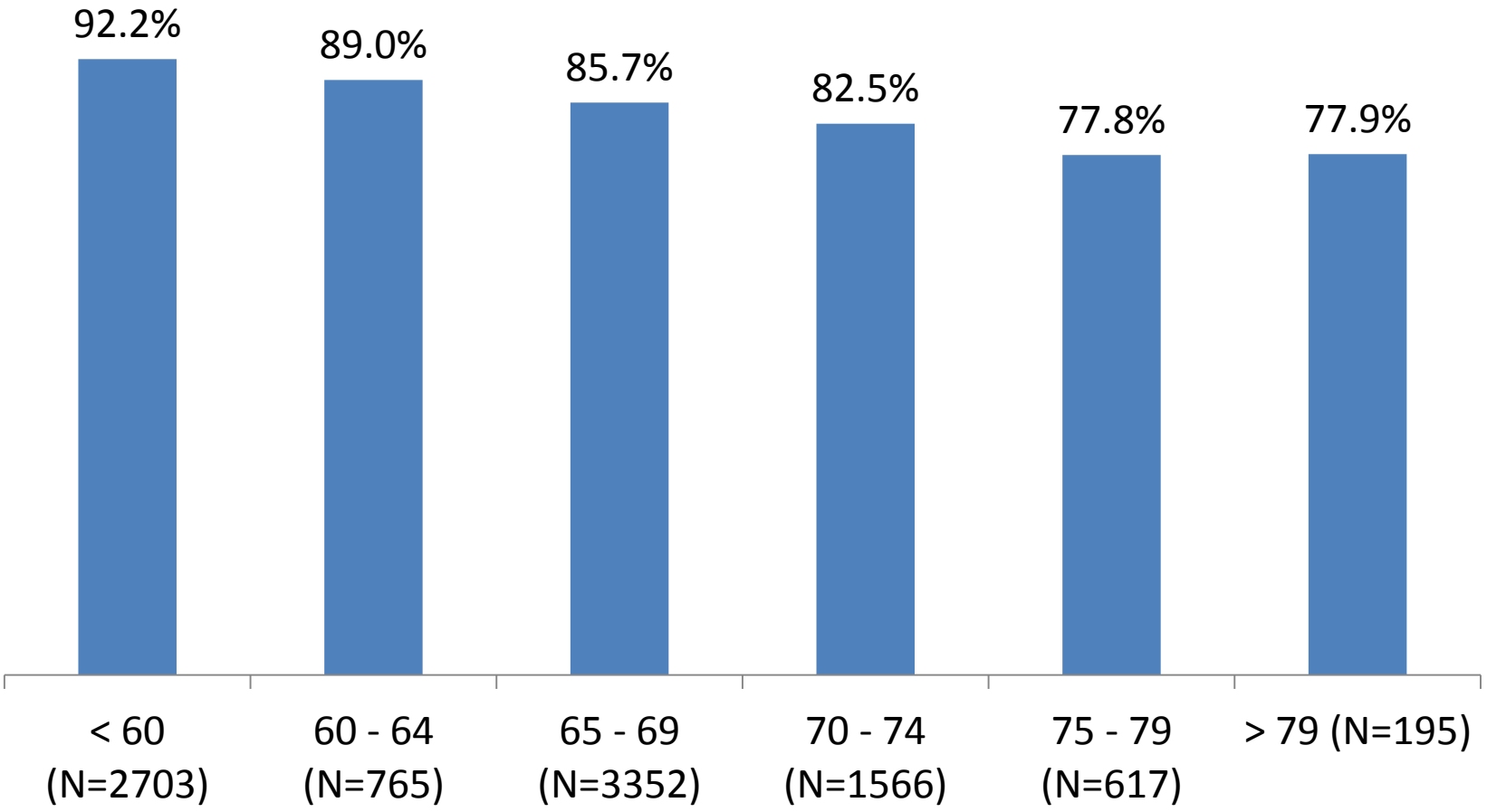
Thank You

Backup Slides Shown

Specificity by Age



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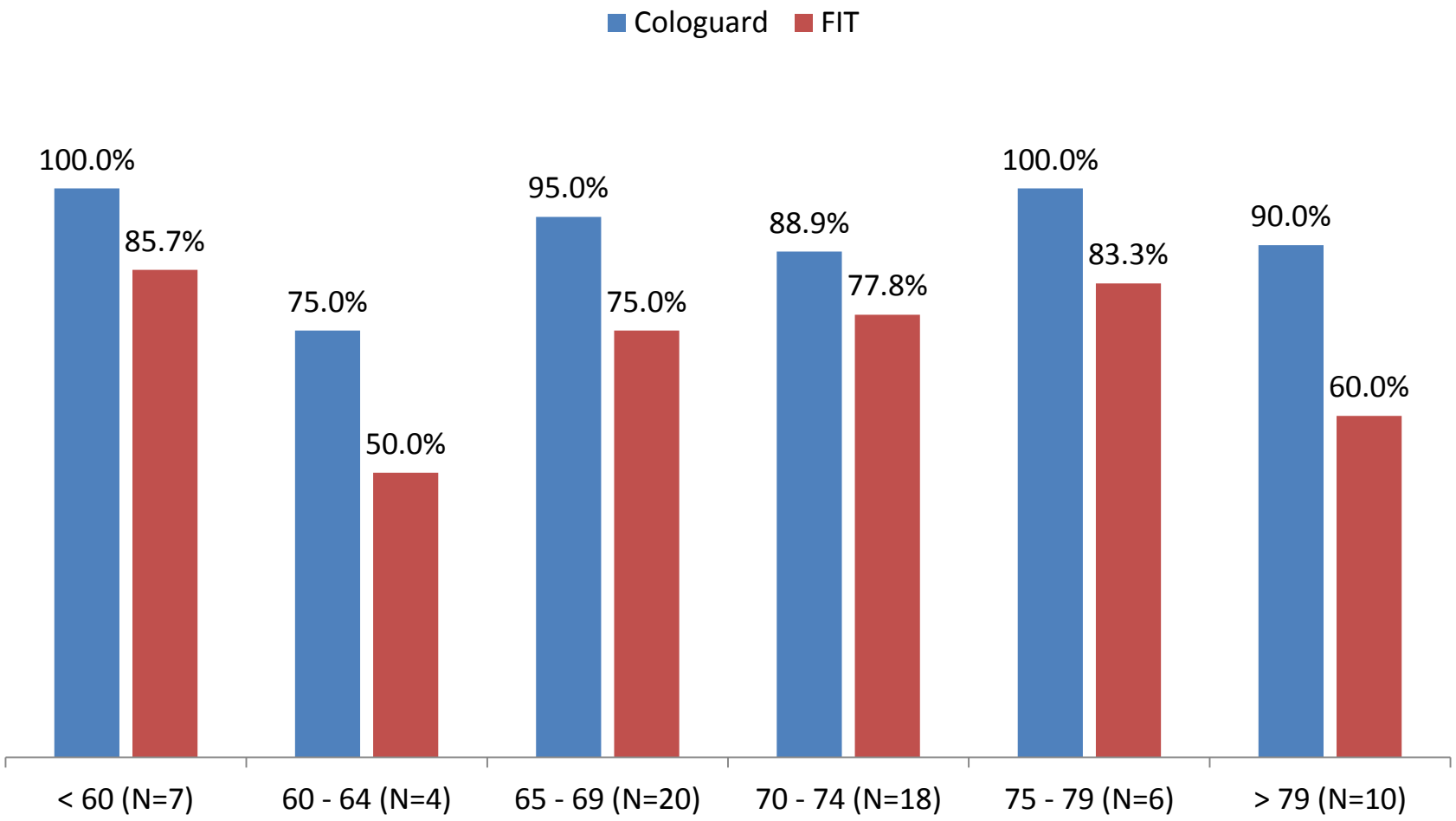
CRC Sensitivity by Age



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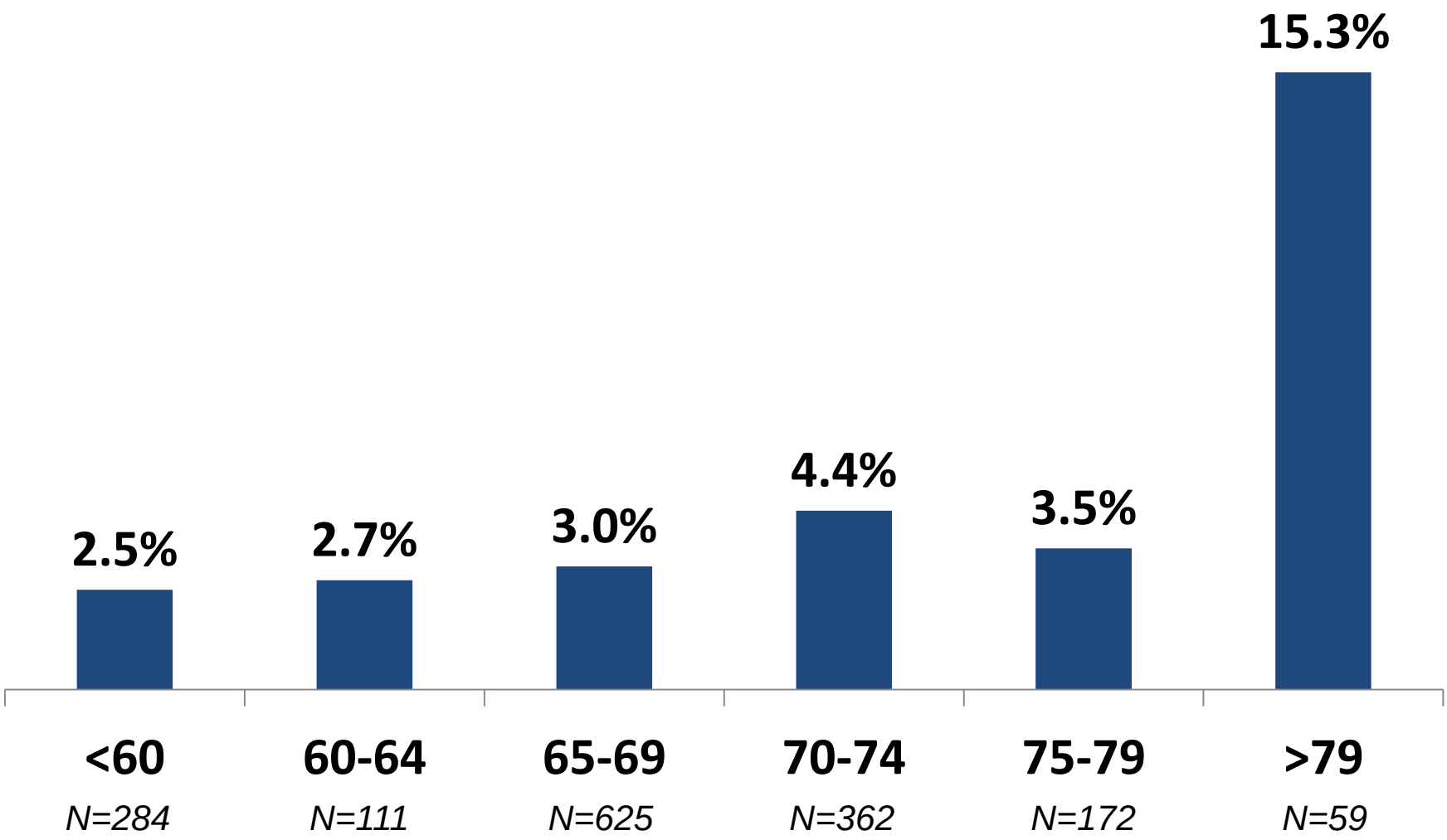
Cologuard CRC PPV by Age



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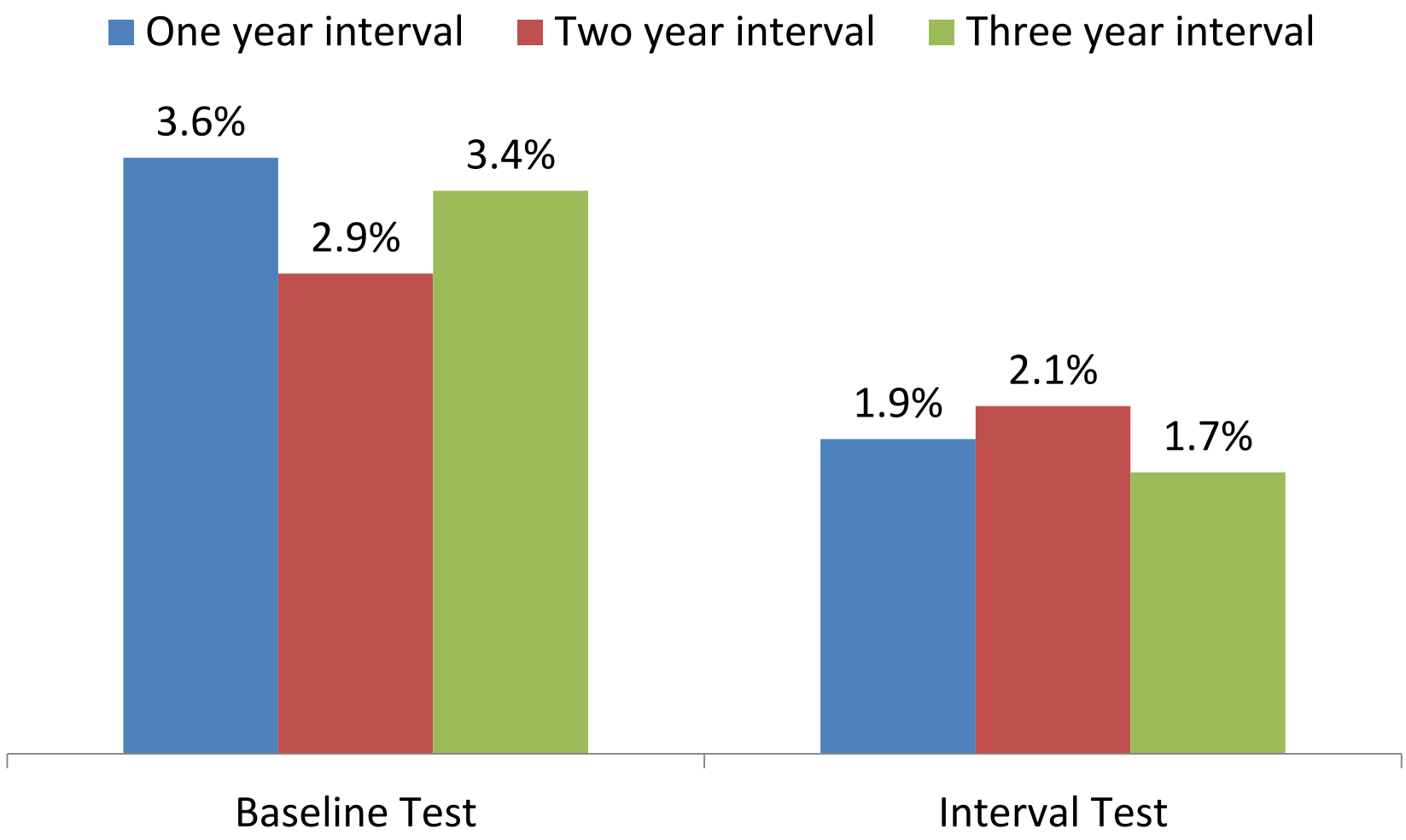
FIT Advanced Neoplasia (CRC + AA) Findings at Different Screening Intervals[1]

(% true positives of those tested)



[1]van Roon, et. al., Gut (2012).

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